(2)

PROPHYLACTIC AND TREATMENT DRUGS FOR ORGANOPHOSPHORUS POISONING

FINAL REPORT

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January 1991

(For Period of September 1984 to 29 March 1990)

Supported by

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06	15		Organophosphinates, organophosphonates, 2-oxo-1,3,2-dioxaphosphorinanes, oximes, carbamates, alkylthiosulfonic acids, synthesis.
07	03		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The program was directed at the design and synthesis of treatment and prophylactic drugs as potential defenses against organophosphorus poisoning. During the past 5.5-year period, 81 compounds were submitted; 20 organophosphinates, 13 carbamates, 12 2-oxo-1,3,2-dioxaphosphorinanes, 7 oximes, 4 organophosphonates, one organophosphate, one phosphonothioate, one phosphinothioate, 4 alkylthiosulfonic acids, 2 chloroalkyl (aryl) carboxylic acids, suberyldicholine dichloride, and 15 other organic compounds.

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FOREWORD

The work described herein was performed under Contract No. DAMD17-84-C-4235 for the U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, Maryland. The report covers the 5.5-year period from 30 September 1984 through 29 March 1990.

A listing of the relevant information for each of the 81 compounds prepared in this 5.5-year program may be found in Table 1 located on page 8 of the report as part of Section 1, "Summary of Work Completed," page 7. Table 1 includes (by compound number (1 through 81 and name)): the sample code numbers, weight in grams, date shipped, bottle number, WRAIR number and the Annual Report reference to the experimental writeup for a representative sample of each compound. Dr. C.L. Stevens served as Principal Investigator, Dr. P. Blumbergs as Associate Investigator, and Dr. A.B. Ash as Program Manager, phone (313) 872-6400.

The purpose of the contract was to maintain and operate a synthesis laboratory to provide chemical compounds needed in the development programs of the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) Edgewood Area, Aberdeen Proving Ground, Maryland.

Citation of commercial organizations and trade names in this report does not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

Acknowledgment

The timely advice and assistance of Dr. Brennie Hackley, Jr., the Contracting Officer's Representative (COR), and Mr. Claire Lieske of the USAMRICD are gratefully acknowledged.

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PROPHYLACTIC AND TREATMENT DRUGS FOR

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1. SUMMARY OF COMPOUNDS PREPARED AND SUBMITTED

This report will summarize work performed, i.e., compounds prepared and submitted, over the 5.5-year period from 30 September 1984 through 29 March 1990. This work has been reported in detail in five Annual Progress Reports covering the following time periods: 30 September 1984 through 29 September 1985 (1), 30 September 1985 through 29 September 1986 (2), 30 September 1986 through 29 September 1987 (3), 30 September 1987 through 29 September 1988 (4), and 30 September 1988 through 29 March 1990 (5).

In this summary report, all of the 81 compounds (88 lots) which were prepared and submitted are listed chronologically in Table 1 by the compound number (1 to 81) and by the chemical name (horizontal headings). Under each of the 81 compounds are listed: code numbers, sample weight in grams and the date shipped (first three vertical columns).

TABLE 1

COMPOUNDS PREPARED AND SUBMITTED UNDER CONTRACT

DAMD17-84-C-4235

30 September 1984 to 29 March 1990

Compound Summary No. and Name (WRAIR Number)

	ASI Lot No.	Wt. (g)	Date Shipped	WRAIR Bottle No. (Wt. to WRAIR)	Experimental Ref. No.	Page No.
1)	Suberyldicholine dichloride					
	RK-04-66	74	10/05/84	BK96326(5 g)	1	53
2)	4-Nitrophenyl methyl(4-trimethylammonio-phenyl)phosphinate trifluoromethylsulfonate					
	PLK-04-192	0.5	10/12/84		1	54
3)	4-Cyanophenyl methyl(4-trimethylammoniophenyl)-phosphinate trifluoromethylfonate					
	PLK-06-262	1.5	10/12/84		1	55
4)	4-Nitrophenyl chloromethyl(2-thienyl)-phosphinate					
	RK-04-59	10	12/25/84	BL05722(5 g)	1	56
5)	4-Trimethylammoniophenyl chloromethyl-(phenyl)phosphinate trifluoromethylsulfonate					
	PLK-06-11	10	10/25/84		1	58
	PLK-06-39	10	2/07/85	BL05759(5 g)	1	58
6)	1-(5-Carboxypentyl)-3-(N,N-dimethyl-carbamyloxy)pyridinium bromide					
	MP-05-72	10	11/26/84		1	59
7)	3-Trimethylammoniopenyl chloromethyl-(phenyl)phosphinate trifluoromethylsulfonate					
	PLK-06-49	1.0	2/07/85		1	60
	CP-01-110	10	6/13/85	BL07879(5 g)	1	60
8)	4-Nitrophenyl methyl(1-naphthyl)phosphinate					
	PLK-06-54	10	2/07/85	BL05731(3 g)	1	60
9)	4-Nitrophenyl methyl (4-methyl-1-naphthyl)phosphinate					
	PLK-06-59	10	2/07/895	BL05740(5 g)	1	61

TABLE 1 (Continued)

	ASI Lot No.	Wt. (g)	Date Shipped	WRAIR Bottle No. (Wt. to WRAIR)	Experimental Ref. No.	Page No.
10)	1-Methyl-3-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)pyridinium iodide					
	GPV-03-84	10	3/06/85	BL05768(5 g)	1	63
	CP-01-301	25	2/12/86		2	39
11)	4-Nitrophenyl methyl(4-trifluoromethylphenyl)phosphinate					
	GPV-03-95	10	3/22/85		1	63
12)	1-(7-Carboxyheptyl)-3-(N,N-dimethylcarbamyloxy)pyridinium bromide					
	MP-05-81	10	3/29/85	BL05777(5 g)	1	65
13)	4-Trimethylammoniophenyl chloromethyl(phenyl)phosphinate chloride					
	PLK-06-80	1.0	4/19/85		1	65
14)	4-Nitrophenyl (1-methoxy-2-naphthyl)-(methyl)phosphinate					
	GPV-03-122	10.5	4/26/85	BL07137(15 g)	1	66
15)	anti-[(Hydroxyimino)methyl]ferrocene					
	CP-01-73	5	6/05/85	BL07744(2.5 g)	1	68
16)	[(Hydroxyimino)methyl]ferrocene (syn, anti-mixture)					
	CP-01-92	5	6/05/85	BL07735(2.5 g)	1	68
17)	1-Propyl-3-(N,N-dimethylcarbamyloxy)-pyridinium iodide					
	CP-01-118	10	6/28/85	BL08107(5 g)	1	69
18)	3-(2-Oxo-1,3,2-dioxaphosphorinan-2-yloxy)-pyridine					
	CP-01-120	10	6/28/85	BL08116(5 g)	1	69
19)	8-(2-Oxo-1,3,2-dioxaphosphorinan-2-yloxy)-quinoline					
	CP-01-133	10	8/07/85	BL09275(5 g)	1	70
20)	1-Methyl-8-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)quinolinium idodide					
	CP-01-158	10	8/07/85	BL09284(5 g)	1	70

TABLE 1 (Continued)

	ASI Lot No.	Wt. (g)	Date Shipped	WRAIR Bottle No. (Wt. to WRAIR)	Experimental Ref. No.	Page No.
21)	4-Nitrophenyl chloromethyl(3-methoxyphenyl)-phosphinate					
	PLK-06-129	10	8/13/85	BL09300(5 g)	1	71
22)	4-Nitrophenyl chloromethyl(4-methoxyphenyl)-phosphinate					
	PLK-06-143	10	9/06/85	BL09677(5 g)	1	72
23)	6-(2-Oxo-1,3,2-dioxaphosphorinan-2-yloxy)-quinoline					
	CP-01-207	10	9/30/85	BL01098(5 g)	1	73
24)	1-Methyl-6-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)quinolinium iodide					
	CP-01-210	10	9/30/85	BL10205(5 g)	1	74
25)	2-Methyl-3-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)quinoline					
	CP-01-231	10	12/17/85	BL12594(5 g)	2	35
26)	4-Aminophenyl N-methylcarbamate					
	CP-01-249	10	12/17/85	BL12585(5 g)	2	36
27)	4-Nitrophenyl ferrocenylmethyl(phenyl)-phosphinate					
	PLK-06-167	7	12/19/85	BL12601(3 g)	2	37
28)	3-Trimethylammoniophenyl methyl(phenyl)-phosphinate trifluoromethylsulfonate					
	PLK-06-205	10	12/19/85	BL12610(5 g)	2	38
29)	4-Trimethylammoniophenyl methyl(phenyl)-phosphinate trifluoromethanesulfonate					
	PLK-06-217	10	1/21/86	BL17946(5 g)	2	39
30)	1-(4-Aminocarbonylpyridinio)-3-(2-hydroxy-iminomethylpyridinio)propane dichloride monohydrate					
	PLK-06-249	8	3/24/86		2	40
31)	2-(4-Dimethylaminophenoxy)-2-oxo-1,3,2-dioxaphosphorinane					
	CP-02-43	7	3/27/86	BK40628(3 g)	2	42
32)	2-Oxo-2-(4-trimethylammoniophenoxy)-1,3,2-dioxaphosphorinane iodide					
	CP-02-22	9	3/27/86	BK40593(3 g)	2	42

TABLE 1 (Continued)

	ASI Lot No.	Wt. (g)	Date Shipped	WRAIR Bottle No. (Wt. to WRAIR)	Experimental Ref. No.	Page No.
33)	2-(2-Dimethylaminophenoxy)-2-oxo-1,3,2-dioxaphosphorinane					
	CP-02-33	20	3/27/86	BK40600(5 g)	2	43
34)	2-Oxo-2-(2-trimethylammoniophenoxy)-1,3,2-dioxaphosphorinane iodide					
	CP-02-37	10	3/27/86	BK40619(5 g)	2	44
35)	1,2-Dimethyl-3-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)quinolinium iodide					
	CP-02-51	5	4/16/86	BL19379(2 g)	2	44
36)	S-2-N,N-Diethyl-N-methylammonioethyl di(1-butyl)-phosphinothioate iodide					
	CP-02-69	10	5/19/86	BL20158(5 g)	2	45
37)	4-Nitrophenyl diphenylphosphinate					
	CP-02-72	20	5/19/86		2	46
38)	(3R,6R)-3,6-Dihydroxytropane 3-(S)(-)-tropate hydrobromide					
	PLK-06-277	13.8	8/15/86		2	47
	CT-1-73-3	34	4/15/87		3	26
39)	S-2-N,N-Diethyl-N-methylammonioethyl O-pinacolyl methylphosphonothioate methylsulfate					
	PLK-06-273	9	8/21/86		2	48
40)	Diethyldi(2-hydroxyethyl)ammonium iodide					
	FJB-01-023	22	9/05/86	BL23604(5 g)	2	48
41)	4-Nitrophenyl 2-furyl(methyl)phosphinate					
	CP-02-205	31	10/01/86		3	21
42)	3-Hydroxy-1-methylpyridinium bromide					
	CP-02-211	12	9/07/86	BL24441	3	22
43)	4-Nitrophenyl dimethylphosphinate					
	CP-02-240	21	11/25/86		3	23
44)	4-Nitrophenyl chloromethyl(2-methoxyphenyl)-phosphinate					
	CP-03-15	10	2/03/87		3	24
45)	3-Nitrophenyl 2-propyl chloromethylphosphonate					
	CP-03-72	10	4/13/87	BL40650(5 g)	3	25

TABLE 1 (Continued)

ASI Lot No.	Wt. (g)	Date Shipped	WRAIR Bottle No. (Wt. to WRAIR)	Experimental Ref. No.	Page No.
46) 4-Nitrophenyl dibutylphosphinate					
CP-03-96-1	8	5/12/87		3	28
CT-1-191	25	1/20/88	BL51162(5 g)	4	32
47) 1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethyl-pyrollo[2,3-b]indol-5-ol (7-carboxy)heptanoate ester					
JD-03-66	1.0	5/12/87		3	29
48) 5-Nonanone oxime					
CP-03-97	5	5/18/87		3	31
49) 2,2'-(4,4'-Biphenylene)bis-[2-hydroxy-4-(2-bromoethyl)morpholine] dihydrobromide					
CT-1-170-17	11	11/23/87	BL50227(5 g)	4	28
50) 3-(Diisopropylphosphato)phenyltrimethyl-ammonium iodide					
CT-1-175	25	12/01/87	BL50389(5 g)	4	31
51) 4-Nitrophenyl 3-(benzoyl)propanesulfonate					
CT-1-236	7.5	2/26/88		4	34
52) 1,3-Dimethyl-3-[2-[N-methyl-N-(7-carboxy-heptanoyl)]aminoethyl]-5-(N-methylcarbamoyloxy)-2,3-dihydroindole hydrochloride					
BSR-01-201	1.5	4/06/88		4	36
BSR-01-207	0.5	4/06/88		4	36
53) 5-Methoxy-3-(2-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-one					
CT-1-287	24	5/05/88	BL52981(5 g)	4	38
54) 3-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-5-methoxy-1,3,4-oxadiazol-2(3H)-one					
CT-1-288	22	5/05/88	BL52972(5 g)	4	40
55) 3-Pyridinealdoxime methiodide					
CT-1-294	21	5/12/88	BL53193(5 g)	4	44
56) [1-(Nonafluorobutyl)pentylidene]hydroxylamine					
CT-1-302	12	5/15/88	BL53577(5 g)	4	44
57) N,N'-Bis(1-methyl-3-pyridinyl)urea diiodide					
CT-2-24	38	8/03/88	BL54583(5 g)	4	46

TABLE 1 (Continued)

	ASI Lot No.	Wt. (g)	Date Shipped	WRAIR Bottle No. (Wt. to WRAIR)	Experimental Ref. No.	Page No.
58)	1-(5-Carboxypentyl)-2-[(hydroxyimino)methyl]-3-methylimidazolium iodide					
	CT-2-60	7	8/25/88	BL54887(3 g)	4	47
59)	5-(1,3,3-Trimethylindolinyl)N,N-diethylcarbamate hydrobromide					
	CT-2-98A	17	11/09/88	BL55982(5 g)	5	31
60)	5-(1,3,3-Trimethylindolinyl)N-ethylcarbamate					
	CT-2-104	12	11/06/88	BL56050(3 g)	5	35
61)	5-(1,3,3-Trimethylindolinyl)N-methylcarbamate					
	CT-2-106	13	11/30/88	BL56210(5 g)	5	36
62)	d_8-Thiodiglycol					
	LVD-01-271	3.0	12/30/88		5	36
	LVD-01-295	3.4	3/14/89		5	36
63)	5-(1,3,3-Trimethylindolinyl)N-heptylcarbamate hydrobromide					
	CT-2-118	17	1/12/89	BL56569(5 g)	5	37
64)	8-Chlorocaprylic acid					
	CT-2-161	7	3/20/89	BL57860(5 g)	5	38
65)	4-(2-Chloroethyl)benzoic acid					
	MB-02-136	6	3/30/89		5	40
66)	5-Carboxypentyl trifluoromethyl disulfide					
	CT-2-168	8.5	4/20/89	BL58170	5	40
67)	cis-4-Chloro-2-buten-1-ol					
	CT-2-173	13	5/08/89	BL59202	5	42
68)	Sodium ethanethiosulfonate					
	CT-2-179	11	5/18/89	BL58876(5 g)	5	42
69)	Thiotaurine					
	BSR-03-155	10	7/17/89	BM00400(5 g)	5	43
70)	Sodium 1-propanethiosulfonate					
	CT-2-195	10.5	7/17/89		5	45
71)	(S)(-)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)carbamate					
	CT-2-192	8.5	8/08/89	BM03554	5	46

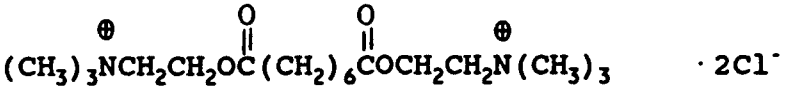
TABLE 1 (Continued)

	ASI Lot No.	Wt. (g)	Date Shipped	WRAIR Bottle No. (Wt. to WRAIR)	Experimental Ref. No.	Page No.
72)	(R)(+)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)carbamate					
	CT-2-197	12	8/08/89	BM00688(3 g)	5	47
73)	5-(1,3,3-Trimethylindolinyl)-N-(3-chlorophenyl)carbamate					
	CT-2-199	15	8/08/89	BM00679(5 g)	5	47
74)	Homothiotaurine					
	BSR-03-184	10	8/08/89	BM00660(5 g)	5	48
75)	4-Chlorobutanol					
	LVD-01-406	20	9/05/89		5	50
76)	5-(1,3,3-Trimethylindolinyl)-N,N-dimethylcarbamate hydrochloride					
	CT-2-220	30	9/25/89	BM01747(5 g)	5	50
77)	6-Aminohexylphosphonic acid, monopinacolyl ester					
	BSR-04-48	2.3	1/11/90	BM04257	5	51
78)	1,3,5-Tris-2'-chloroethylbenzene					
	CT-2-295	2.5	2/20/90	BM 03858	5	54
79)	Methyl pinacolyl 4-(4-carboxybutanoylamino)-benzylphosphonate					
	CT-2-289	5.0	3/06/90	BM04257	5	57
80)	Monopinacolyl 4-(4-carboxybutanoylamino)-benzylphosphonate					
	CT-2-298	2.5	3/06/89	BM04266	5	61
81)	(5-Carboxypentyl)(3,3-dimethylbutyl)-phosphinic acid					
	BSR-04-153	5.0	4/02/90		5	62

2. DISCUSSION OF WORK COMPLETED

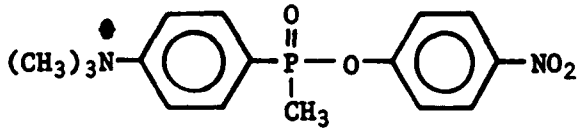
The 81 compounds completed in the 5.5-year duration of the contract are discussed below.

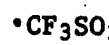
2.1 Suberyldicholine dichloride



The four-step synthetic route to the title compound is shown in Chart No. 1. The starting material, suberoyl dichloride (1), was prepared in 80% yield by treatment of suberic acid with oxalyl chloride in refluxing benzene. Intermediate 3 was prepared by a two-step literature procedure (6). Thus, acid chloride 1 was warmed with excess dimethylaminoethanol to give the diester 2 in 70% yield. Quaternization of ester 2 with ethyl iodide gave suberyldicholine diiodide (3) in 91% yield. The diiodide salt 3 was converted to the dichloride salt 4 by passage through a Dowex 2-X8 column (chloride ion form). Recrystallization of the crude title compound from dimethylformamide gave dichloride 4 as a white, crystalline, hygroscopic solid, mp 200-201°C (d), which required recrystallization from isopropanol-ethyl acetate to give analytically pure title compound in 66% yield.

2.2 4-Nitrophenyl methyl(4-trimethylammoniophenyl)phosphinate trifluoromethylsulfonate





The title compound is a new structure not reported in the chemical literature. This phosphinate ester is the second member of a series of water-soluble esters that are being developed by Ash Stevens Inc. The synthesis of this compound, prepared by the route developed earlier for the synthesis of the analogous 4-chlorophenyl phosphinate ester (7), is shown in Chart No. 2. Thus treatment of methyl 4-dimethylaminophenyl(methyl)phosphinate (7) with one equivalent of sodium hydroxide followed by one equivalent of hydrochloric acid gave phosphinic acid 1. Phosphinate ester 2 was prepared in 82% yield by heating a mixture of crude acid 1, 4-nitrophenol and dicyclohexyl-carbodiimide in ethyl acetate. The dimethylamino group in ester 2 could not be quaternized with methyl iodide, but treatment with

CHART NO. 1

SUBERYLDICHOLINE DICHLORIDE

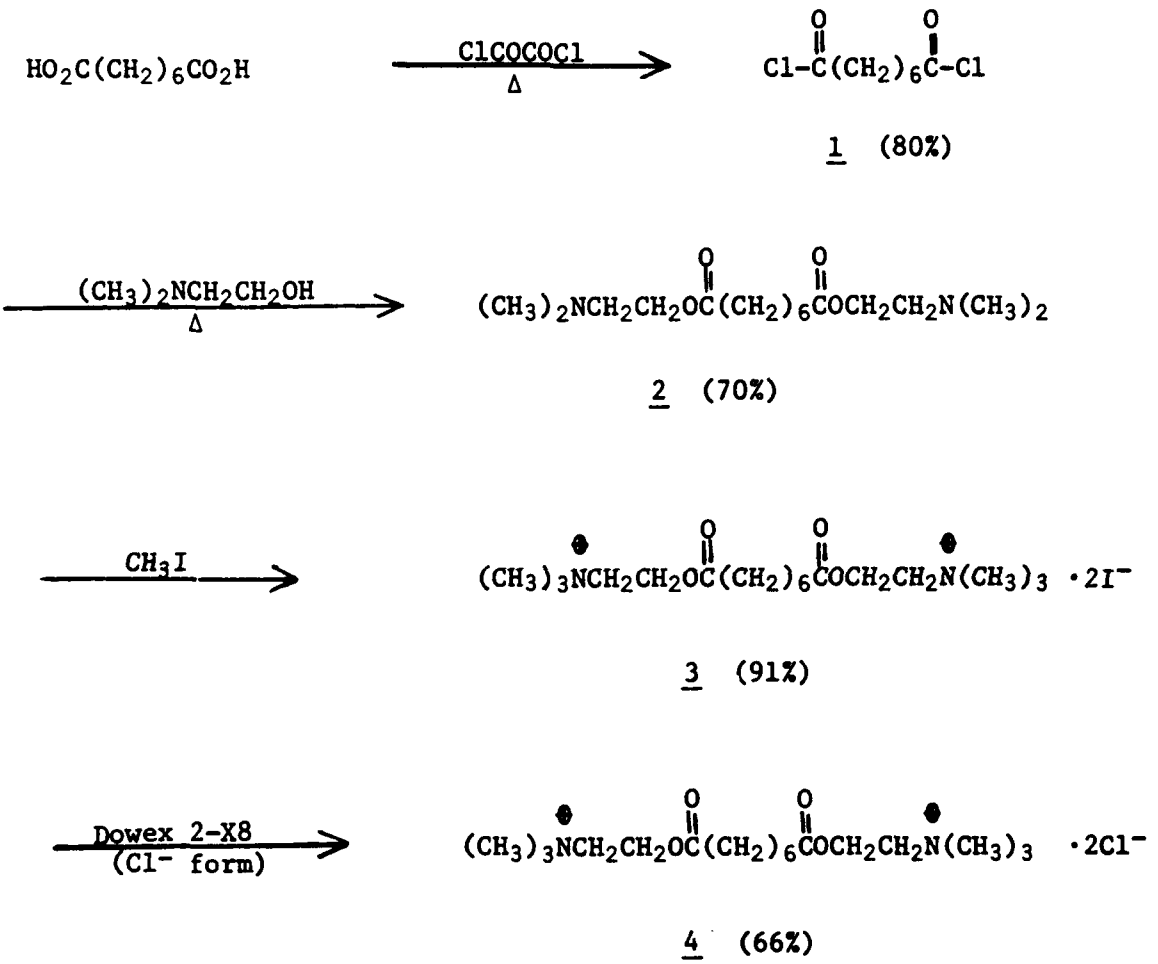
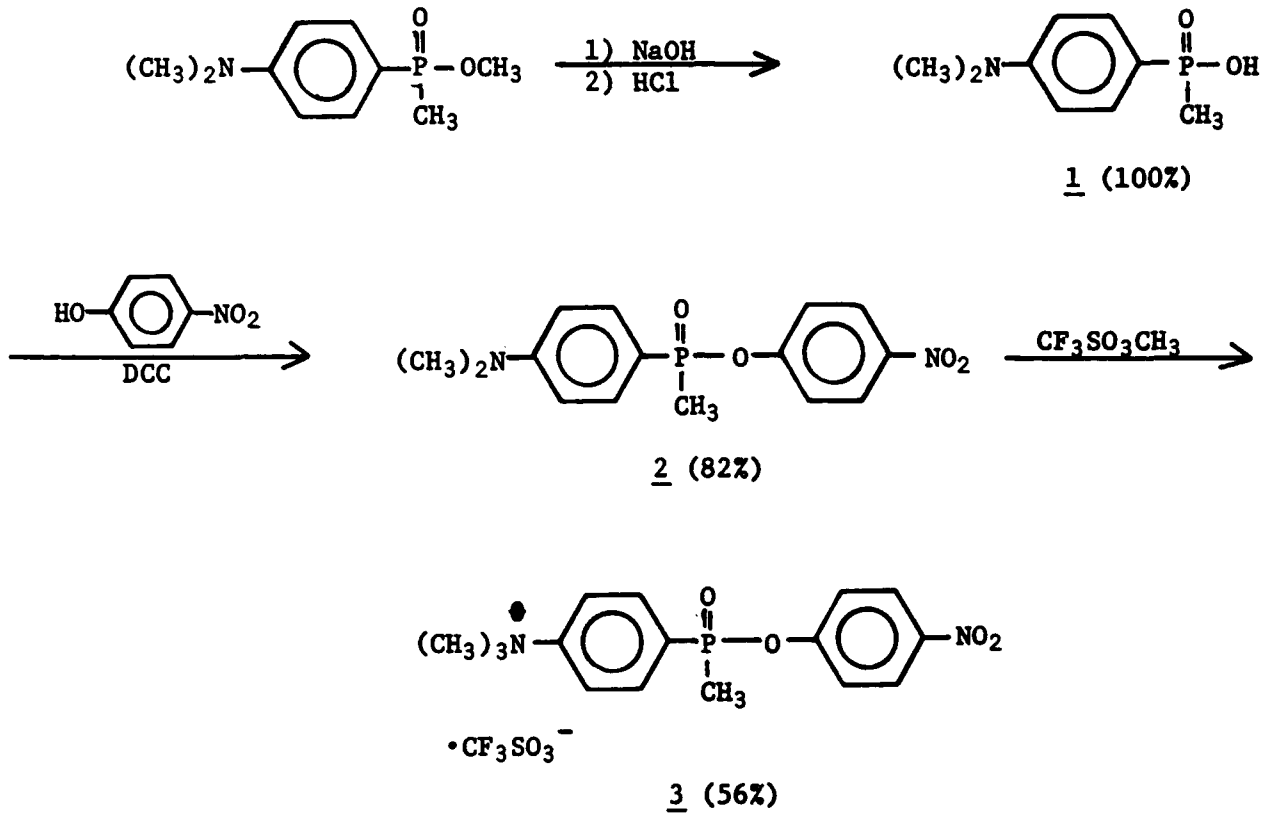


CHART NO. 2

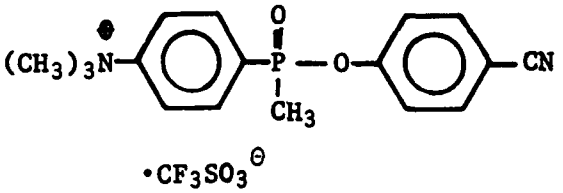
4-NITROPHENYL METHYL(4-TRIMETHYLAMMONIOPHENYL)-PHOSPHINATE TRIFLUOROMETHYLSULFONATE



methyl trifluoromethylsulfonate gave the title compound in 56% yield.

The title phosphinate ester is freely soluble in water and has a half-life of 11.3 min in 0.10 M MOPS buffer at pH 7.60 and 25°C.

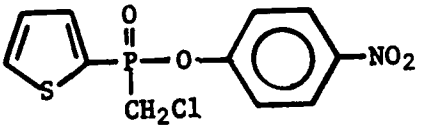
2.3 4-Cyanophenyl methyl(4-trimethylammoniophenyl)phosphinate trifluoromethylsulfonate



The title compound is a new structure not reported in the chemical literature. This phosphinate ester is the third member of a series of water-soluble esters under development by Ash Stevens Inc. The preparation route utilized for the 4-nitrophenyl ester (see section 2.2) was used also for this compound as shown in Chart No. 3. The 4-cyanophenyl ester 3 was obtained in 24% overall yield.

The title phosphinate ester is freely water-soluble and has a half-life of 21 min in 0.10 M MOPS buffer at pH 7.60 and 25°C.

2.4 4-Nitrophenyl chloromethyl(2-thienyl)phosphinate



The title compound is a new structure not reported in the chemical literature. The preparative route for this compound, outlined in Chart No. 4, follows a general procedure developed in these laboratories for the synthesis of chloromethyl-substituted phosphinates. This route requires the acquisition of 2-thienylphosphonous dichloride (2) as a key intermediate. The literature reports the synthesis of the dichloride by the Friedel-Crafts reaction of thiophene with phosphorus trichloride catalyzed by stannic chloride (8).

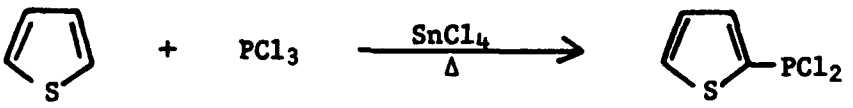
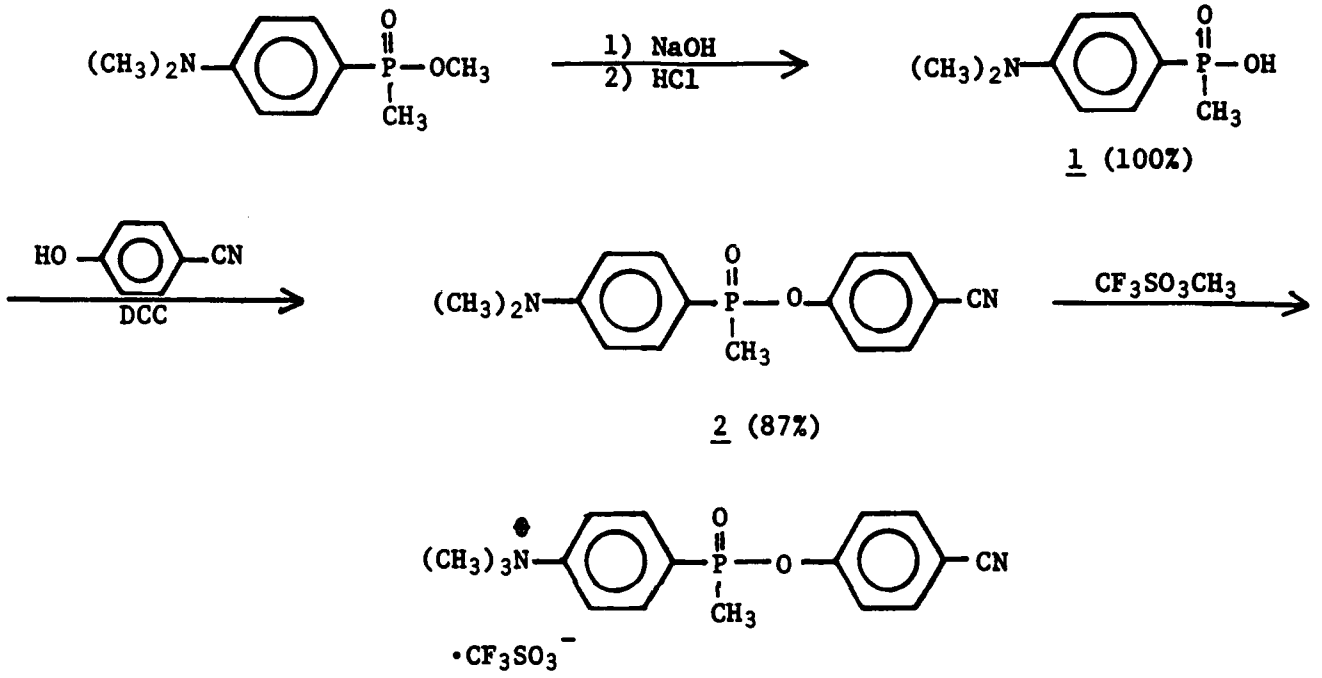


CHART NO. 3

4-CYANOPHENYL METHYL(4-TRIMETHYLAMMONIOPHENYL)-PHOSPHINATE TRIFLUOROMETHYLSULFONATE



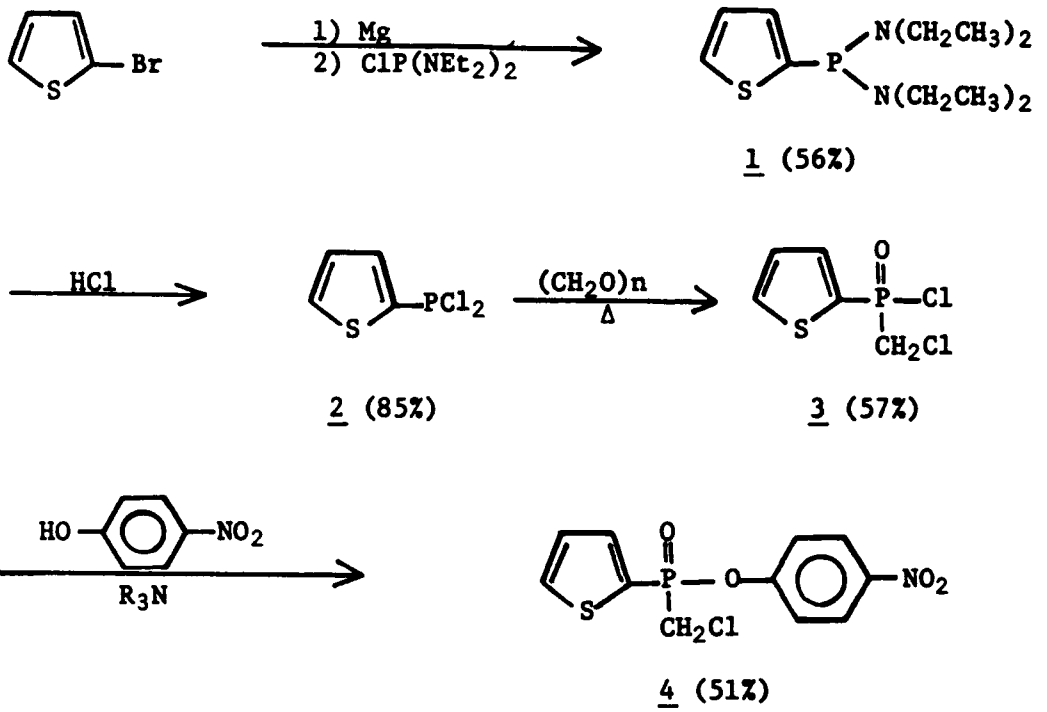
1 (100%)

2 (87%)

3 (28%)

CHART NO. 4

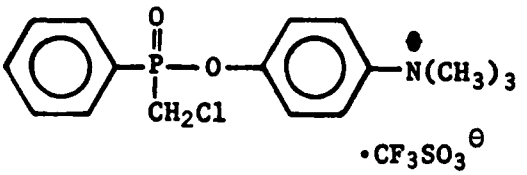
4-NITROPHENYL CHLOROMETHYL(2-THIENYL)PHOSPHINATE



In our study, however, this procedure gave extremely low yields (9), so an alternate route to intermediate 2 was developed. The Grignard reagent, prepared from the reaction of 2-bromothiophene with magnesium, was treated with bis(diethylamino)chlorophosphine to give intermediate 1 in 56% yield. Conversion of the phosphonous diamide 1 to the required phosphonous dichloride 2 was accomplished with anhydrous hydrogen chloride in ether in 85% yield. Treatment of intermediate 2 with excess paraformaldehyde at 130°C gave chloromethylphosphinic chloride 3; which was esterified with 4-nitrophenol in the presence of ethyldiisopropylamine to give the title compound 4 in 51% yield.

The title 4-nitrophenyl ester has a half-life of 54 at pH 7.60 in 0.10 M MOPS buffer at 25°C.

2.5 4-Trimethylammoniophenyl chloromethyl(phenyl)phosphinate trifluoromethylsulfonate



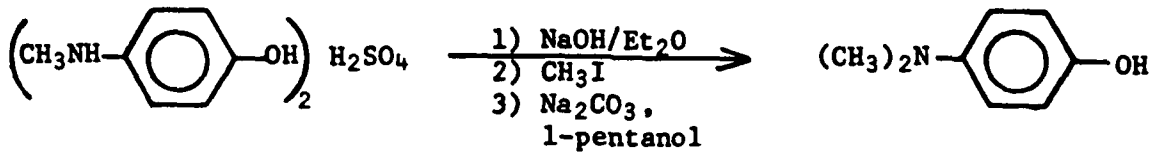
A 0.75 g sample of the title compound was prepared earlier, under a prior contract (7), using the procedure shown in Chart No. 5. This same procedure was used for current resynthesis.

4-Dimethylaminophenol (1) was prepared from 4-methylaminophenol sulfate by a standard literature method (10). Chloromethyl(phenyl)phosphinic acid was resynthesized by a procedure described in an earlier report (11). The phosphinic acid and phenol were coupled with dicyclohexylcarbodiimide in ethyl acetate to give phosphinate 2 in 60% yield. Intermediate 2 could not be quaternized by treatment with methyl iodide, but treatment of ester 2 with methyl trifluoromethylsulfonate in methylene chloride gave the quaternary ester 3 in 48% yield.

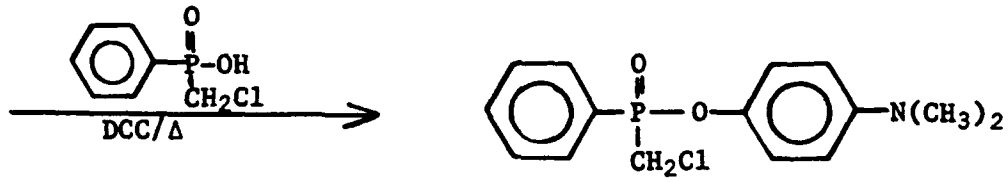
The title phosphinate ester is freely soluble in water and has a half-life of 98 min at pH 7.60 in 0.10 M MOPS buffer at 25°C.

CHART NO. 5

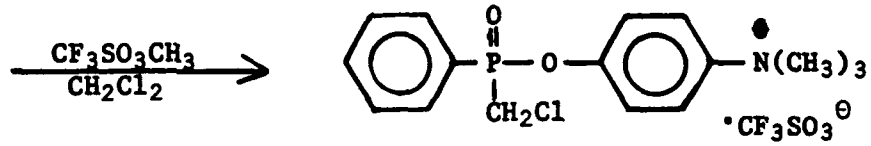
4-TRIMETHYLAMMONIOPHENYL CHLOROMETHYL(PHENYL)-PHOSPHINATE TRIFLUOROMETHYLSULFONATE



1 (64%)

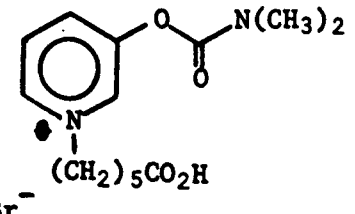


2 (60%)

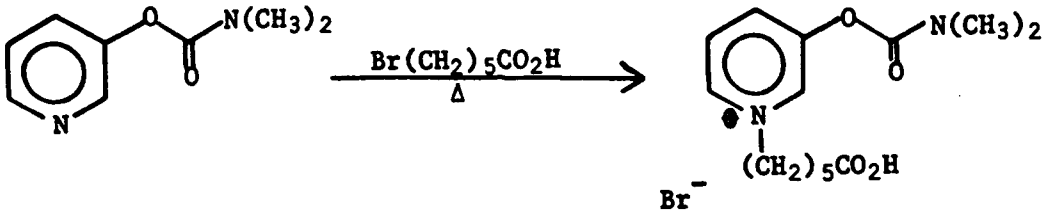


3 (48%)

2.6 1-(5-Carboxypentyl)-3-(N,N-dimethylcarbamyloxy)pyridinium bromide

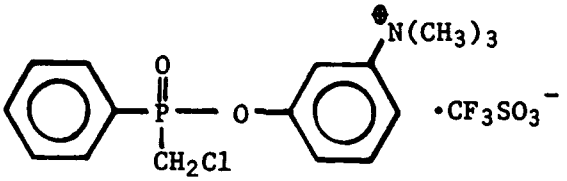


The title compound is a new structure not reported in the chemical literature. The one-step procedure shown below was developed for the preparation of this compound. Thus, 3-pyridyl-N,N-dimethylcarbamate, prepared under a prior contract (11), was



coupled with commercially available 6-bromohexanoic acid to give a fairly pure product which was purified by cellulose-column chromatography to give pure title compound in 59% yield.

2.7 3-Trimethylammoniophenyl chloromethyl(phenyl)phosphinate trifluoromethylsulfonate

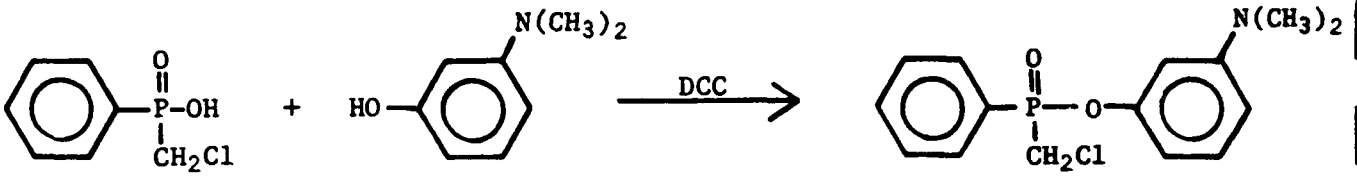


The title compound is a new structure not reported in the chemical literature. This compound is the second member of a series of water-soluble phosphinate esters under development by Ash Stevens Inc. in which the water-solubilizing quaternary ammonium substituent is located on the phenolic leaving group. The synthesis route shown in Chart No. 6 parallels the route used for the preparation of the 4-trimethylammonio-substituted analog (see section 2.5).

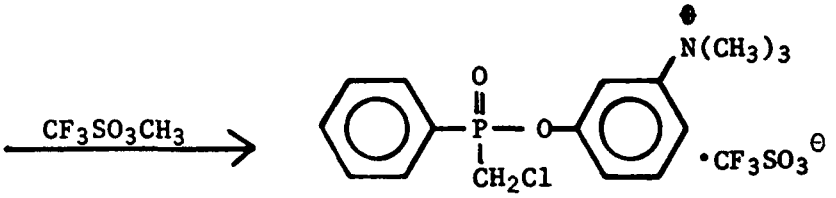
Chloromethyl(phenyl)phosphinic acid was resynthesized by a procedure described in an earlier report (11), and this compound was coupled with commercially available 3-dimethylaminophenol using dicyclohexylcarbodiimide in methylene chloride as an esterifica-tion reagent to give ester 1 in 52% yield. Although the reaction was very slow, phosphinate ester 1 could be quarternized by treatment with a large excess of methyl iodide.

CHART NO. 6

3-TRIMETHYLAMMONIOPHENYL CHLOROMETHYL(PHENYL)-PHOSPHINATE TRIFLUOROMETHYLSULFONATE



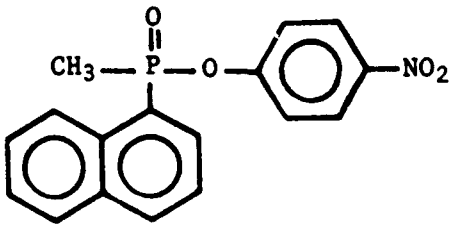
1 (52%)



2 (67%)

However, treatment of phosphinate ester 1 with one equivalent of methyl trifluoromethylsulfonate was found to be more advantageous and gave the title quaternary ammonium phosphinate ester 2 as a trifluoromethylsulfonate salt in 78% yield.

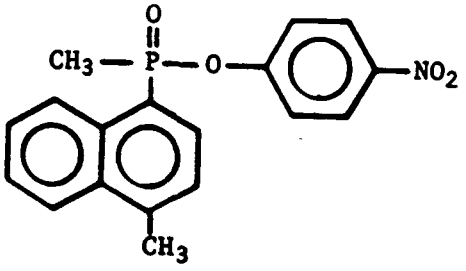
2.8 4-Nitrophenyl methyl(1-naphthyl)phosphinate



The title compound is a new structure not previously reported in the chemical literature. The preparative route for this compound, outlined in Chart No. 7, follows a general procedure developed in these laboratories for the synthesis of aryl-substituted methylphosphinates.

The Grignard reagent, prepared from 1-bromonaphthalene, was treated with N,N-diethyl-P-methylphosphonamidic, chloride and the resulting phosphinic amide was hydrolyzed with aqueous hydrochloric acid in dioxane to give the phosphinic acid 1 in 32% yield. Esterification of acid 1 with 4-nitrophenol and dicyclohexylcarbodiimide gave the title phosphinic acid ester 2 in 57% yield.

2.9 4-Nitrophenyl methyl(4-methyl-1-naphthyl)phosphinate



The title compound is a new structure not previously reported in the chemical literature. The same general synthetic procedure used for the preparation of the 1-naphthyl-substituted phosphinate ester (section 2.8) was used also in this case, as shown in Chart No. 8.

The Grignard reagent prepared from 1-bromo-4-methyl-naphthalene was treated with N,N-diethyl-P-methylphosphonamidic chloride. The resulting amide was hydrolyzed with aqueous hydrochloric acid to give the phosphinic acid 1 in 33% yield. Intermediate 1 was converted to the title ester 2 by treatment with 4-nitrophenol and dicyclohexylcarbodiimide in 62% yield.

CHART NO. 7

4-NITROPHENYL METHYL(1-NAPHTHYL)PHOSPHINATE

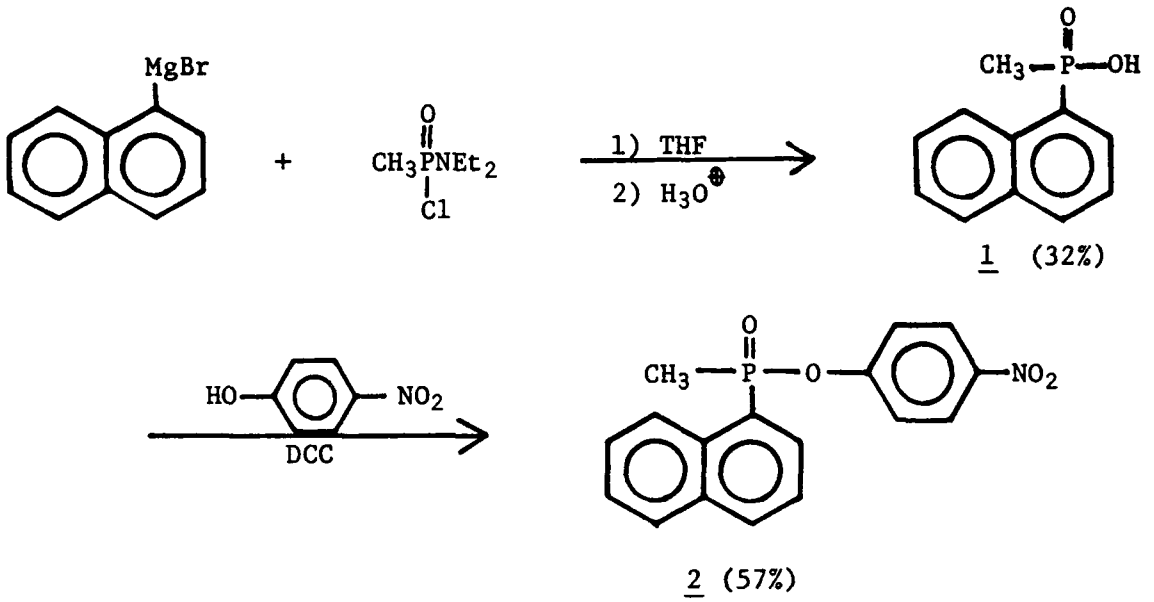
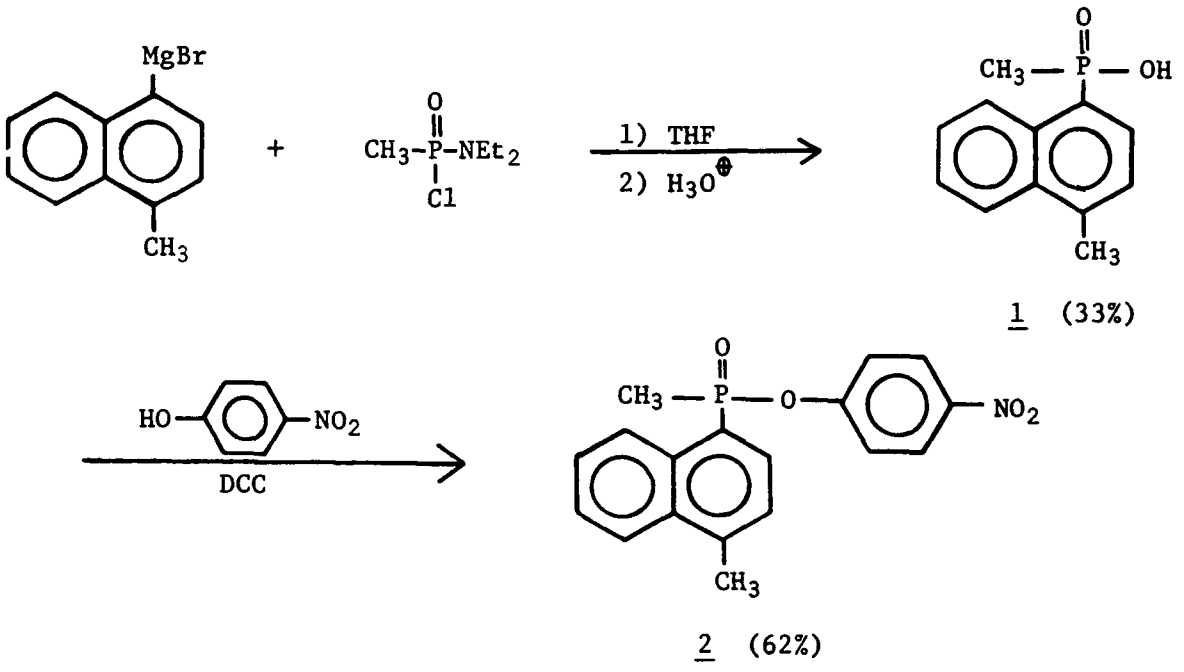
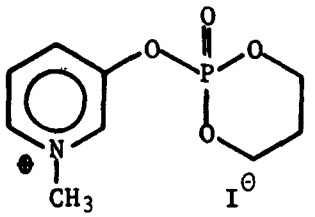


CHART NO. 8

4-NITROPHENYL METHYL(4-METHYL-1-NAPHTHYL)PHOSPHINATE



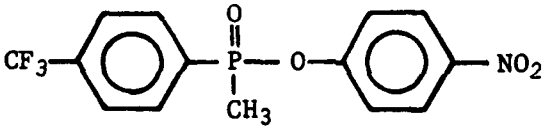
2.10 1-Methyl-3-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)-pyridinium iodide



The title structure is a new compound not previously reported in the chemical literature. The three-step synthetic route shown in Chart No. 9 was used for the preparation of two samples, 10 g (3/85) and 25 g (2/86).

Treatment of phosphorus oxychloride with one equivalent of 1,3-propanediol, following a literature procedure (12), gave the cyclic 2-chlorophosphorinane 1 in 38% yield. The acid chloride 1 was mixed with 3-hydroxypyridine and triethylamine to give cyclic phosphorus ester 2 in 44% and 53% yields. Quaternization of intermediate 2 with iodomethane in acetonitrile gave the title compound 3 in 59% and 52% yields as an iodide salt.

2.11 4-Nitrophenyl methyl(4-trifluoromethylphenyl)phosphinate



A 10 g sample of the title compound was prepared by Ash Stevens Inc. under a prior contract (13). This sample was subsequently found to be heavily contaminated with a phosphonate ester byproduct. Therefore, for the current resynthesis, the alternative preparation route shown in Chart No. 10 was devised to eliminate formation of phosphonate byproducts.

The Grignard reagent, prepared from 4-bromobenzotrifluoride was treated with N,N-diethyl-P-methylphosphonamide to give the phosphinamide 1 in 42% yield. Intermediate 1 was hydrolyzed with aqueous hydrochloric acid in dioxane to produce the corresponding phosphinic acid 2 in 53% yield. Treatment of acid 2 with 4-nitrophenol and dicyclohexylcarbodiimide gave the title phos-phinate ester 3 in 52% yield, free from phosphonate impurities.

CHART NO. 9

1-METHYL-3-(2-OXO-1,3,2-DIOXAPHOSPHORINAN-2-YLOXY)PYRIDINIUM IODIDE

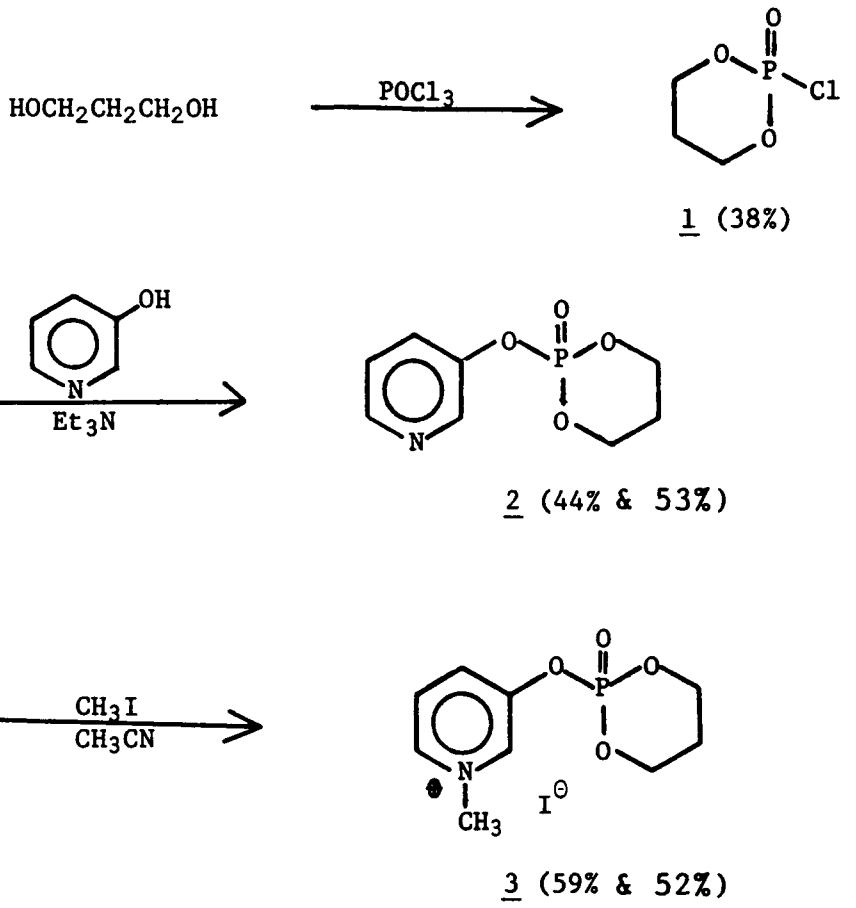
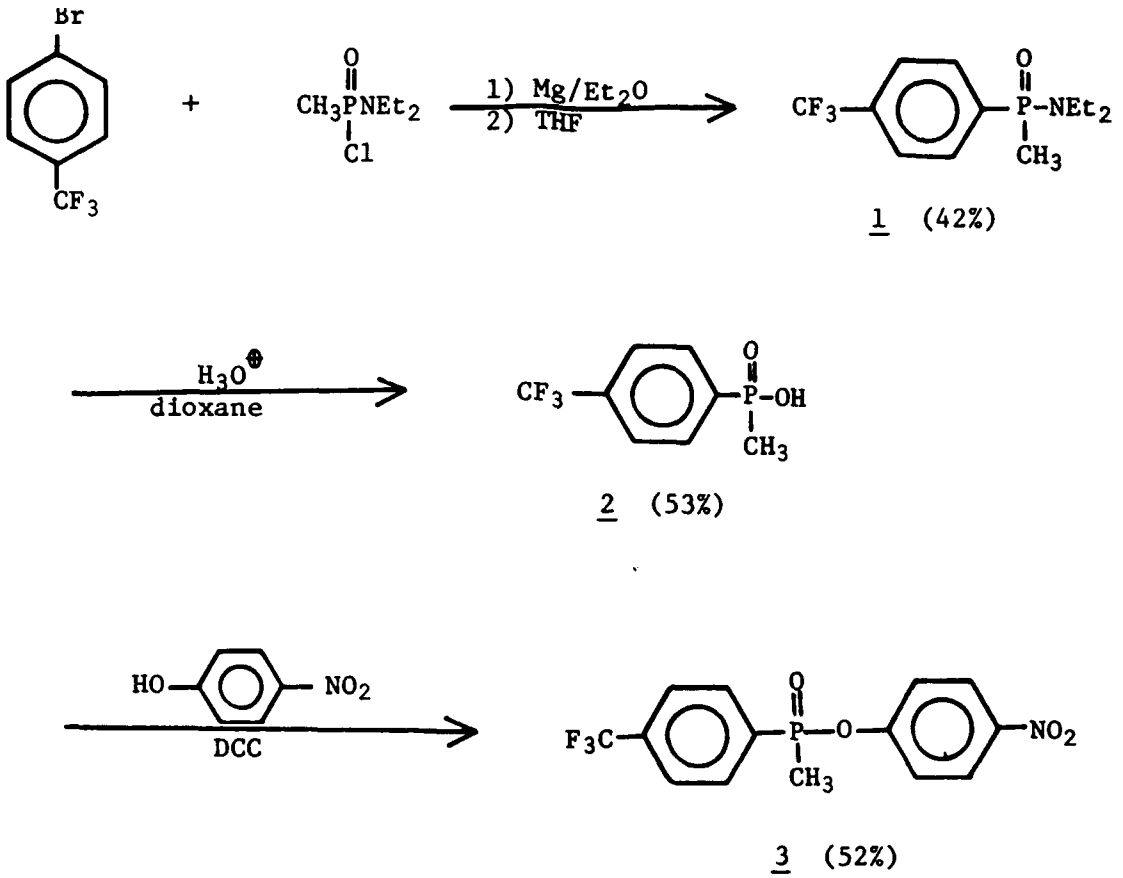
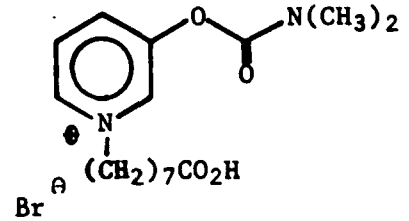


CHART NO. 10

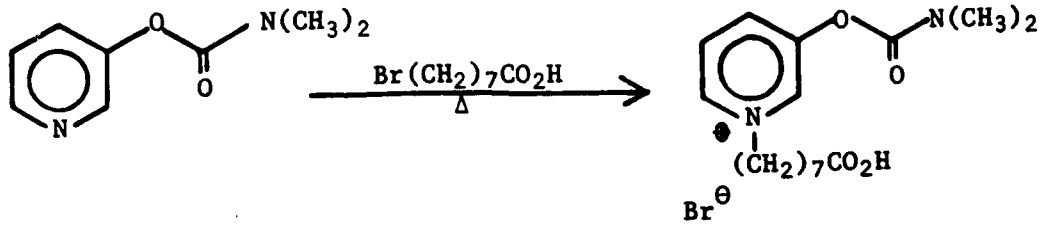
4-NITROPHENYL METHYL(4-TRIFLUOROMETHYLPHENYL)PHOSPHINATE



2.12 1-(7-Carboxyheptyl)-3-(N,N-dimethylcarbamyloxy)pyridinium bromide

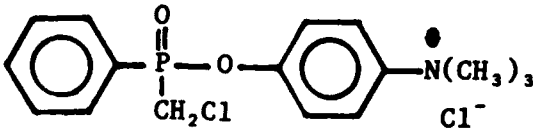


The title compound was prepared by a similar one-step procedure such as that used to prepare the 1-(5-carboxypentyl)-substituted analog (see section 2.6).



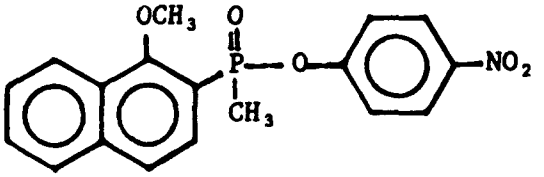
Thus, 3-pyridyl-N,N-dimethylcarbamate, prepared under a prior contract (11), was treated with commercially available 8-bromooctanoic acid to give fairly pure title compound. This material was purified by cellulose chromatography and several recrystallizations to give analytically pure product.

2.13 4-Trimethylammoniophenyl chloromethyl(phenyl)phosphinate chloride



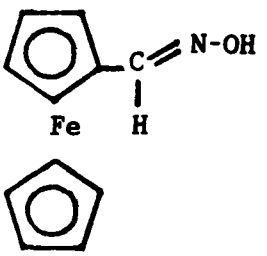
The title compound, chloride salt, was prepared by passing the corresponding trifluoromethylsulfonate salt (section 2.5) over a Dowex 2-X8 (chloride form) ion-exchange resin column. Four columns, each containing approximately 15 equivalents of ion-exchange resin, were necessary to obtain complete conversion to the chloride salt in 33% yield. The title phosphinate salt is hygroscopic and freely soluble in water.

2.14 4-Nitrophenyl (1-methoxy-2-naphthyl)(methyl)phosphinate



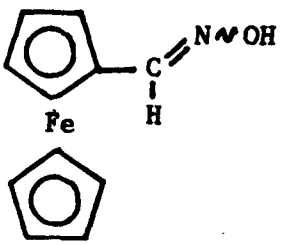
The title compound is a new structure previously unreported in the chemical literature. The synthetic route to the title compound is shown in Chart No. 11. Following a literature procedure (14), 1-naphthol was brominated by a bromine-t-butylamine complex to give 2-bromo-1-naphthol (1) in 54% yield. Methylation of naphthol 1 with dimethyl sulfate (15) gave intermediate 2 in 58% yield. Bromonaphthalene 2 was treated with magnesium to prepare the Grignard reagent which was coupled with N,N-diethyl-P-methylphosphonamidic chloride, and the resulting phosphinamide was hydrolyzed to phosphinic acid 3 in 40% yield. Esterification of acid 3 with 4-nitrophenol and dicyclohexyl-carbodiimide gave the title phosphinate ester 4 in 56% yield.

2.15 anti-[(Hydroxyimino)methyl]ferrocene



The title compound was prepared as shown in Chart No. 12 by heating ferrocene carboxaldehyde with hydroxylamine in aqueous ethanol (16) to give a mixture of syn- and anti-isomers, compounds 1 and 2. Fractional crystallization from benzene gave the more stable anti-isomer 2 in 17% overall yield.

2.16 [(Hydroxyimino)methyl]ferrocene (syn, anti-mixture)



The title compound, a 1:1 mixture of syn- and anti-isomers, was prepared by the condensation of hydroxyl amine with ferrocene carboxaldehyde, as shown in Chart No. 12.

CHART NO. 11

4-NITROPHENYL 1-METHOXY-2-NAPHTHYL(METHYL)PHOSPHINATE

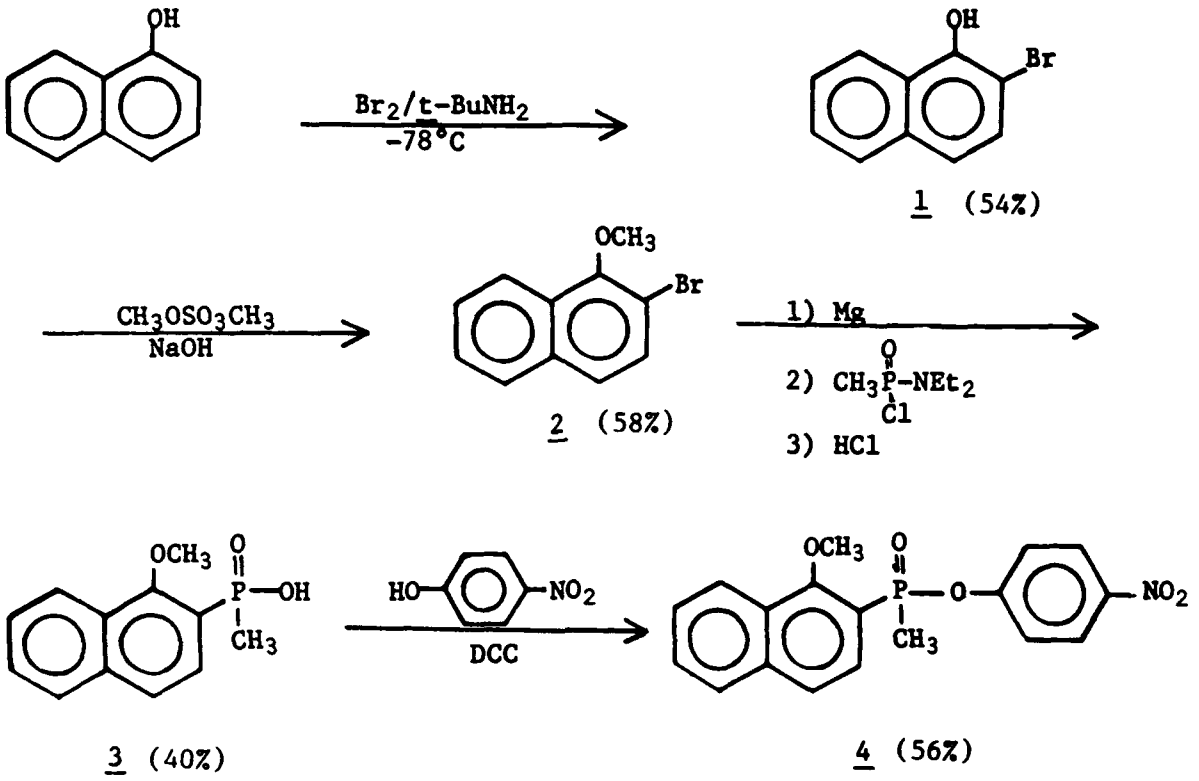
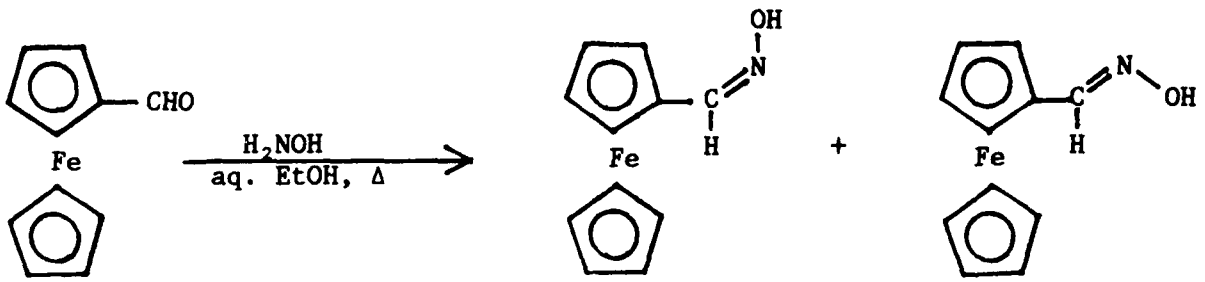


CHART NO. 12

[(HYDROXYIMINO)METHYL]FERROCENE

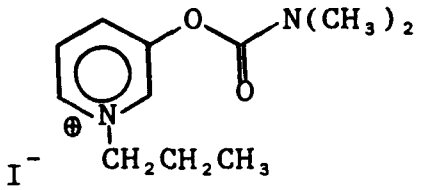


1 syn

2 anti

Crystallization of the concentrated mother liquors from the fractional crystallization of the anti-isomer (section 2.15) gave the title material in 17% overall yield.

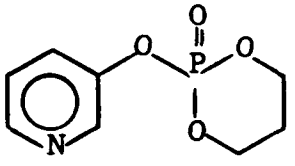
2.17 1-Propyl-3-(N,N-dimethylcarbamyloxy)pyridinium iodide



The title compound, a pyridostigmine analog, is not reported in the chemical literature. A two-step synthesis route to this compound is shown in Chart No. 13 and follows a general literature procedure for similar pyridostigmine analogs (17). Condensation of 3-hydroxypyridine with dimethylcarbamyl chloride gave carbamate 1 in 84% yield. Alkylation of intermediate 1 with 1-iodopropane gave the title compound 2 as the iodide salt in 72% yield as a light yellow crystalline solid.

Attempts to prepare the bromide salt of 2 either by the alkylation of carbamate 1 with 1-bromopropane or by the exchange of iodide ion for bromide ion in 2 by ion-exchange resin, gave compound 2 bromide salt as a non-crystalline extremely hygroscopic yellow oil.

2.18 3-(2-Oxo-1,3,2-dioxaphosphorinan-2-yloxy)pyridine

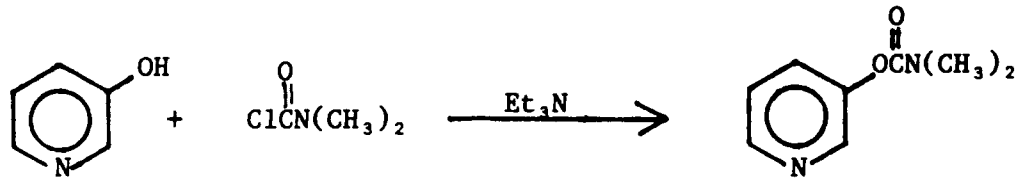


The title compound was an intermediate in the synthesis route for the previously prepared N-methylated analog (section 2.10). The same procedure was used for the current resynthesis, as shown in Chart No. 9.

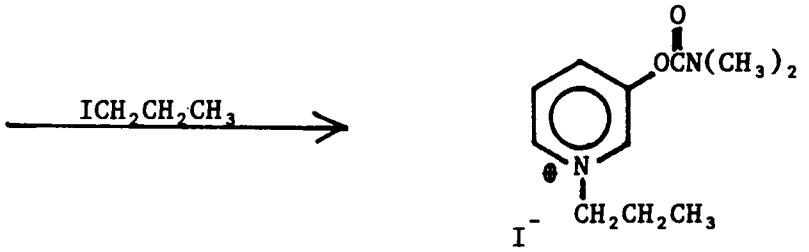
A sufficient quantity of intermediate 1 was on hand from the previous synthesis, so only the final step of the synthesis route was repeated. Condensation of intermediate 1 with 3-hydroxypyridine with triethylamine as a base gave the title phosphorinane 2 in 49% yield.

CHART NO. 13

1-PROPYL-3-(N,N-DIMETHYLCARBAMYLOXY)PYRIDINIUM IODIDE

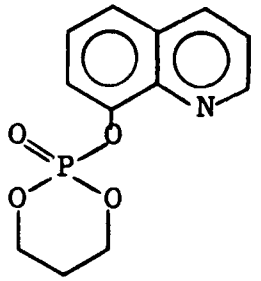


1 (84%)



2 (72%)

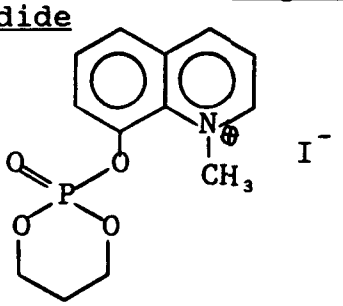
2.19 8-(2-Oxo-1,3,2-dioxaphosphorinan-2-yloxy)quinoline



This structure is a new compound not previously reported in the chemical literature. The title compound is an intermediate in the synthesis of the corresponding quaternized methyl iodide derivative (section 2.20), the preparation of which is shown in Chart No. 14.

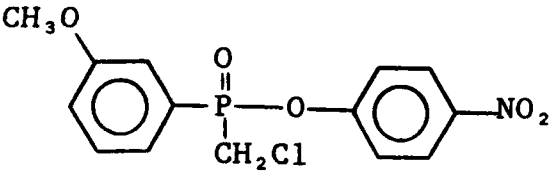
Commercially available 8-quinolinol was treated with 2-chloro-2-oxo-1,3,2-dioxaphosphorinane (section 2.10) and triethylamine to give cyclic phosphorinanyl ester 1 in 37% yield after recrystallization.

2.20 1-Methyl-8-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)-quinolinium iodide



As stated above, the synthetic sequence to this target structure is shown in Chart No. 14. Treatment of intermediate 1 (section 2.19) with excess methyl iodide in refluxing acetonitrile gave the desired quaternary product 2 in 38% yield.

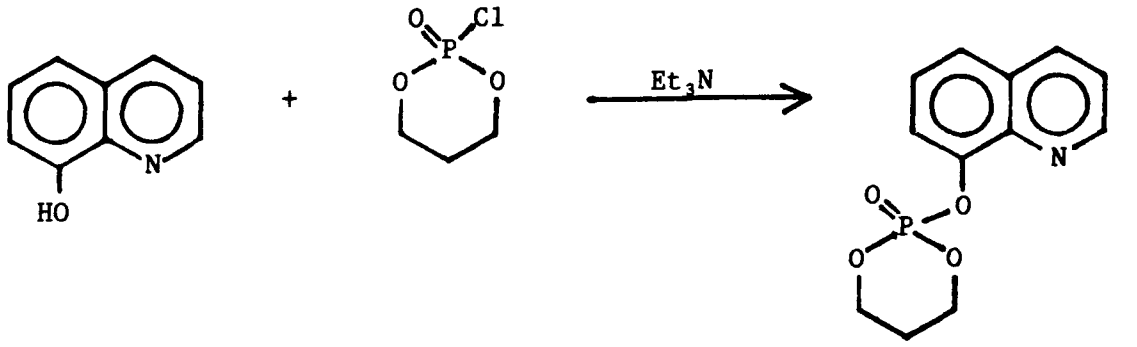
2.21 4-Nitrophenyl chloromethyl(3-methoxyphenyl)phosphinate



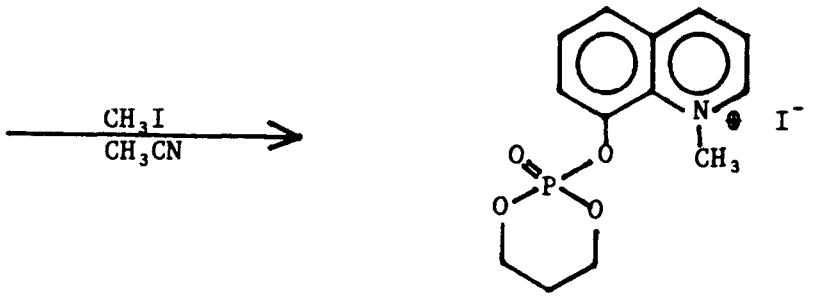
The four-step synthetic sequence to this new phosphinate ester is shown in Chart No. 15 and follows the general route used to prepare the 2-methoxy analog (11). The Grignard reagent, prepared from 3-bromoanisole, was treated with bis(diethylamino) chlorophosphine followed by ethereal hydrogen chloride to give phosphonous dichloride 1 in 46% yield. Treatment of intermediate 1 with excess paraformaldehyde gave chloromethyl(phenyl)-

CHART NO. 14

8-(2-OXO-1,3,2-DIOXAPHOSPHORINAN-2-YLOXY)QUINOLINE AND
1-METHYL-8-(2-OXO-1,3,2-DIOXAPHOSPHORINAN-2-YLOXY)QUINOLINIUM IODIDE



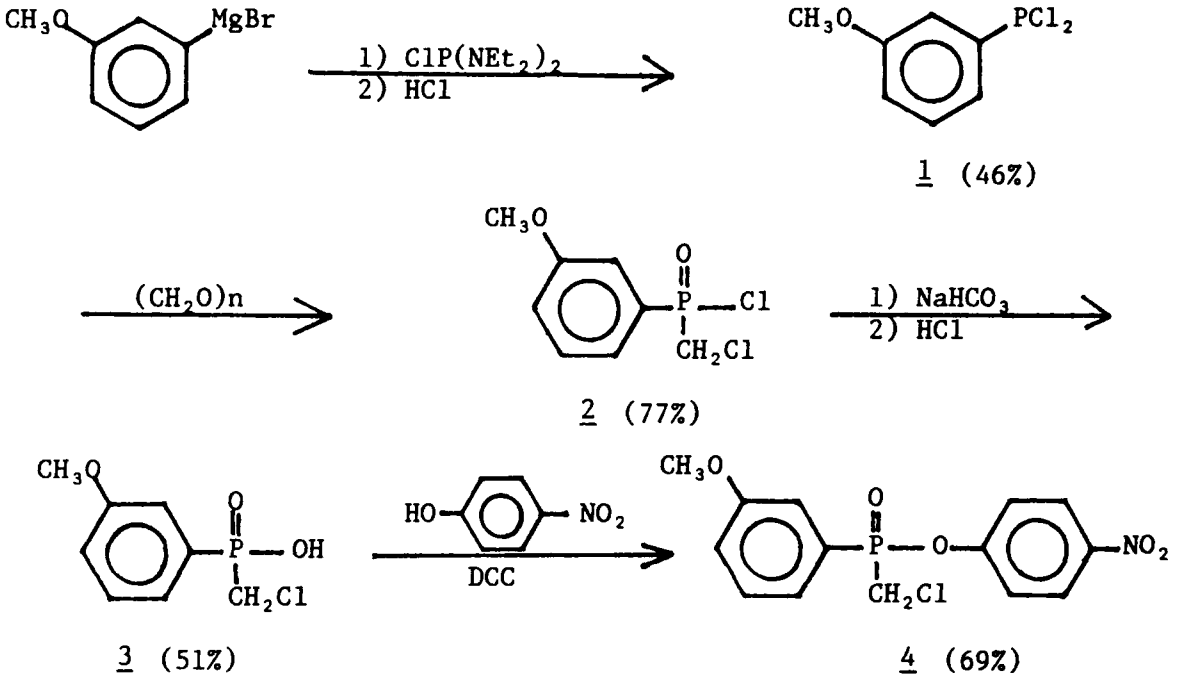
1 (37%)



2 (38%)

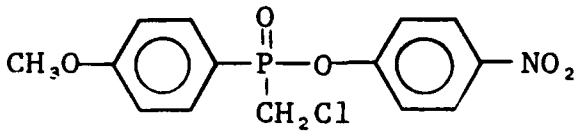
CHART NO. 15

4-NITROPHENYL CHLOROMETHYL(3-METHOXYPHENYL)PHOSPHINATE



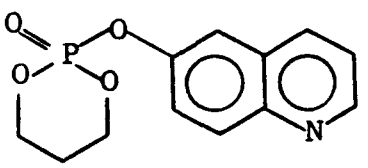
phosphinic chloride (2, 77%). Compound 2 was hydrolyzed to the phosphinic acid 3 which was purified via the dicyclohexylamine salt. Esterification of phosphinic acid 3 with 4-nitrophenol and dicyclohexylcarbodiimide gave the title compound 4 in 69% yield.

2.22 4-Nitrophenyl chloromethyl(4-methoxyphenyl)phosphinate



The synthesis route to the title phosphinate ester is shown in Chart No. 16 and follows the general procedure used to prepare the 3-methoxyphenyl analog (section 2.21). 4-Methoxyphenylphosphonous dichloride (1) was prepared by a literature procedure (18) by heating anisole with phosphorus trichloride and stannic chloride. Reaction of intermediate 1 with paraformaldehyde gave chloromethyl(4-methoxyphenyl)phosphinic chloride. Attempts to purify this material failed. Accordingly, the acid chloride was hydrolyzed to the phosphinic acid 2 which was then purified via the dicyclohexylamine salt. Esterification of intermediate 2 with 4-nitrophenol and dicyclohexylcarbodiimide gave the title phosphinate ester 3 in 60% yield.

2.23 6-(2-Oxo-1,3,2-dioxaphosphorinan-2-yloxy)quinoline



The title compound is a new structure not previously reported in the chemical literature. This compound is an intermediate in the synthesis of the corresponding quaternized methyl iodide derivative (section 2.24), the preparation of which is shown in Chart No. 17. Following a literature procedure (19) 6-methoxyquinoline was heated with concentrated hydrobromic acid to give 6-quinolinol (1) in 61% yield. 6-Quinolinol (1) was treated with 2-chloro-2-oxo-1,3,2-dioxaphosphorinane (section 2.10) and triethylamine to give the cyclic phosphorinanyl ester 2 in 59% yield.

CHART NO. 16

4-NITROPHENYL CHLOROMETHYL(4-METHOXYPHENYL)PHOSPHINATE

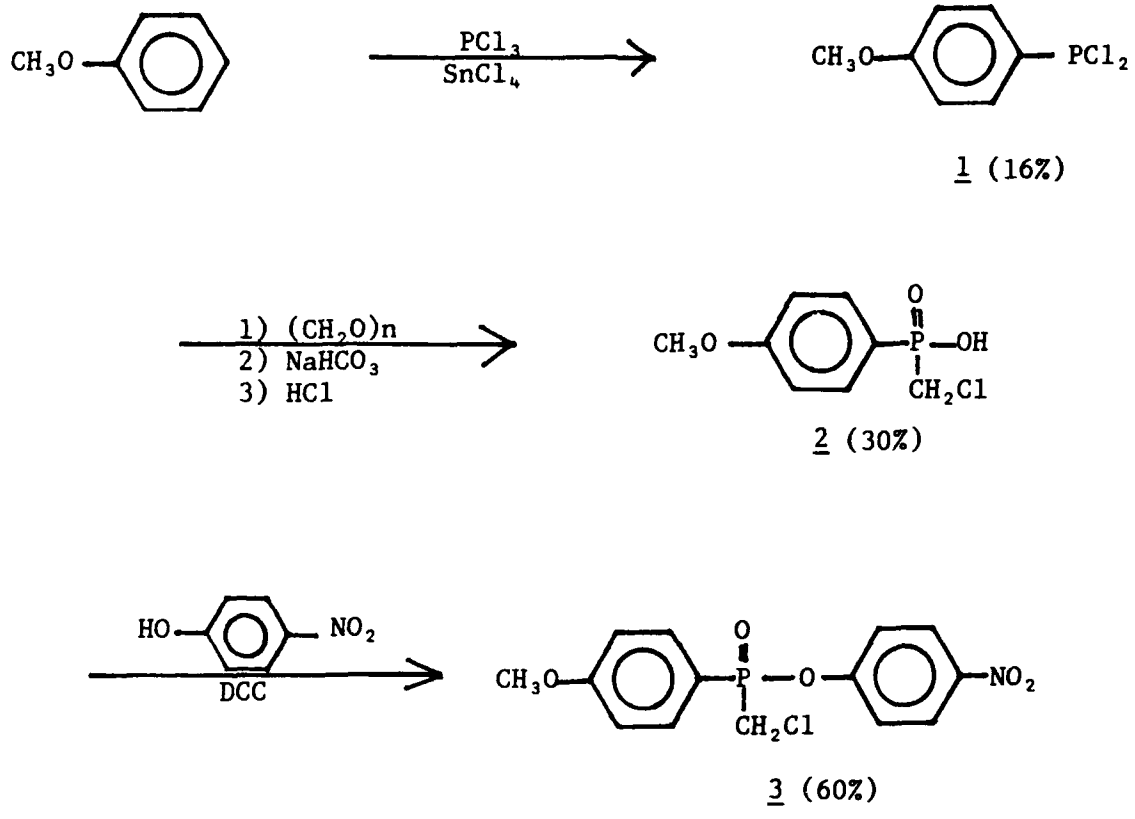
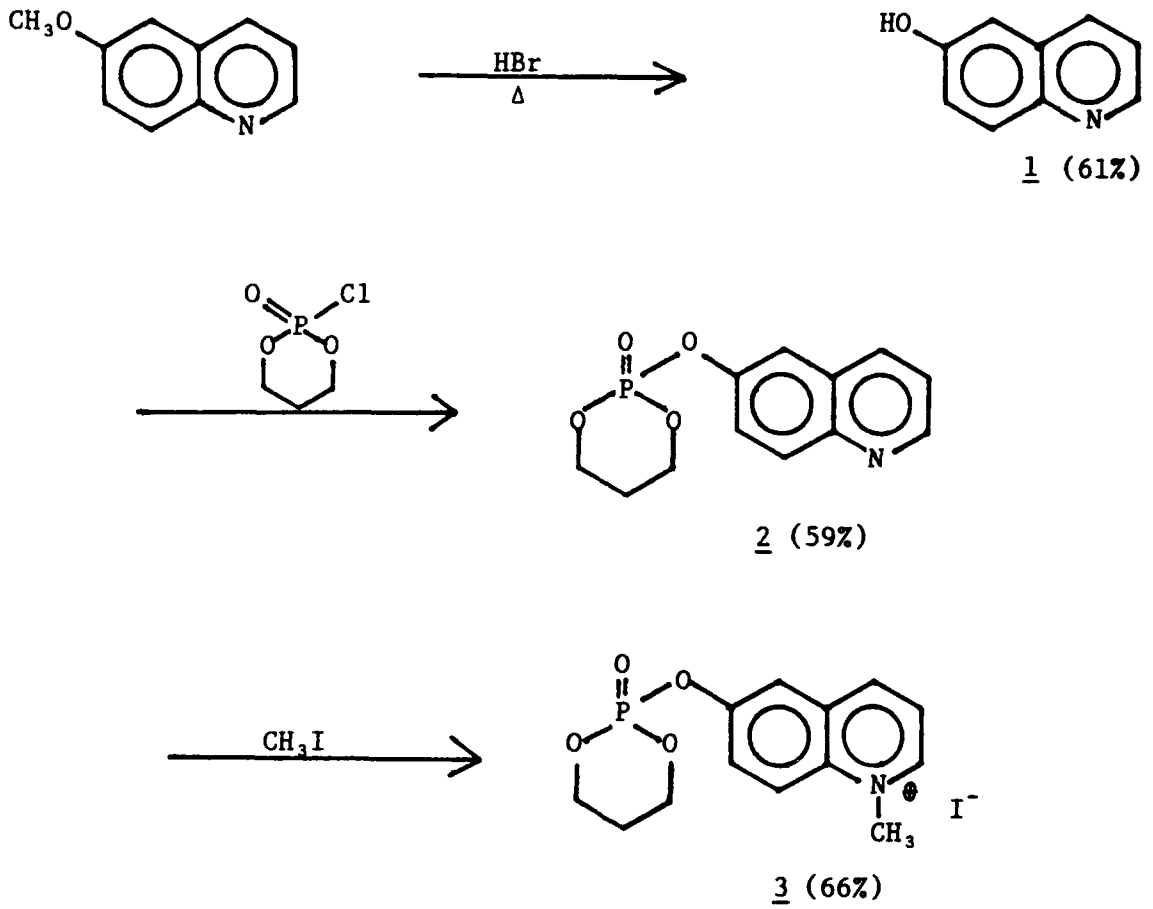
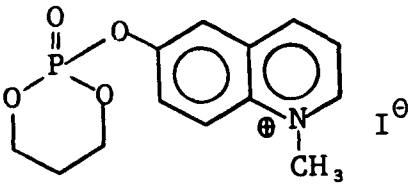


CHART NO. 17

6-(2-OXO-1,3,2-DIOXAPHOSPHORINAN-2-YLOXY)QUINOLINE AND
1-METHYL-6-(2-OXO-1,3,2-DIOXAPHOSPHORINAN-2-YLOXY)QUINOLINIUM IODIDE

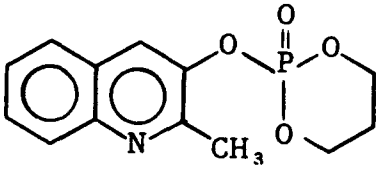


2.24 1-Methyl-6-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)-quinolinium iodide



The title compound is a new structure not previously reported in the chemical literature. As stated above, the route to the title compound is shown in Chart No. 17. Intermediate 2 was methylated with excess methyl iodide in acetonitrile to give the title quinolinium ester 3 in 66% yield.

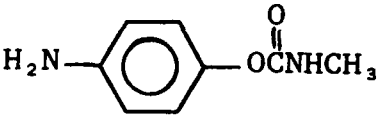
2.25 2-Methyl-3-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)-quinoline



The title compound represents a new structure that is not reported in the chemical literature. This material is an intermediate in the preparation of the quaternary N-methyl iodide salt 3 discussed in section 2.35. The synthesis route is shown in Chart No. 18.

2-Methyl-3-quinolinol (1) was prepared in 66% yield by thermal decarboxylation of the corresponding 4-quinoline carboxylic acid in Dowtherm at 215°C. Treatment of quinolinol 1 with 2-chloro-2-oxo-1,3,2-dioxaphosphorinane (12) gave the title compound 2 in 63% yield.

2.26 4-Aminophenyl N-methylcarbamate



The title compound was prepared by a modified literature procedure (20,21) outlined in Chart No. 19. Thus, 4-nitrophenol was treated with methyl isocyanate and a catalytic amount of triethylamine to give N-methylcarbamate 1 in 43% yield after recrystallization. Intermediate 1 was hydrogenated at 3 atmospheres in acetic acid with 10% palladium on carbon catalyst to give the title carbamate 2 in 32% yield after purification.

CHART NO. 18

2-METHYL-3-(2-OXO-1,3,2-DIOXAPHOSPHORINAN-2-YLOXY)QUINOLINE AND
1,2-DIMETHYL-3-(2-OXO-1,3,2-DIOXAPHOSPHORINAN)-2-YLOXY)QUINOLINIUM IODIDE

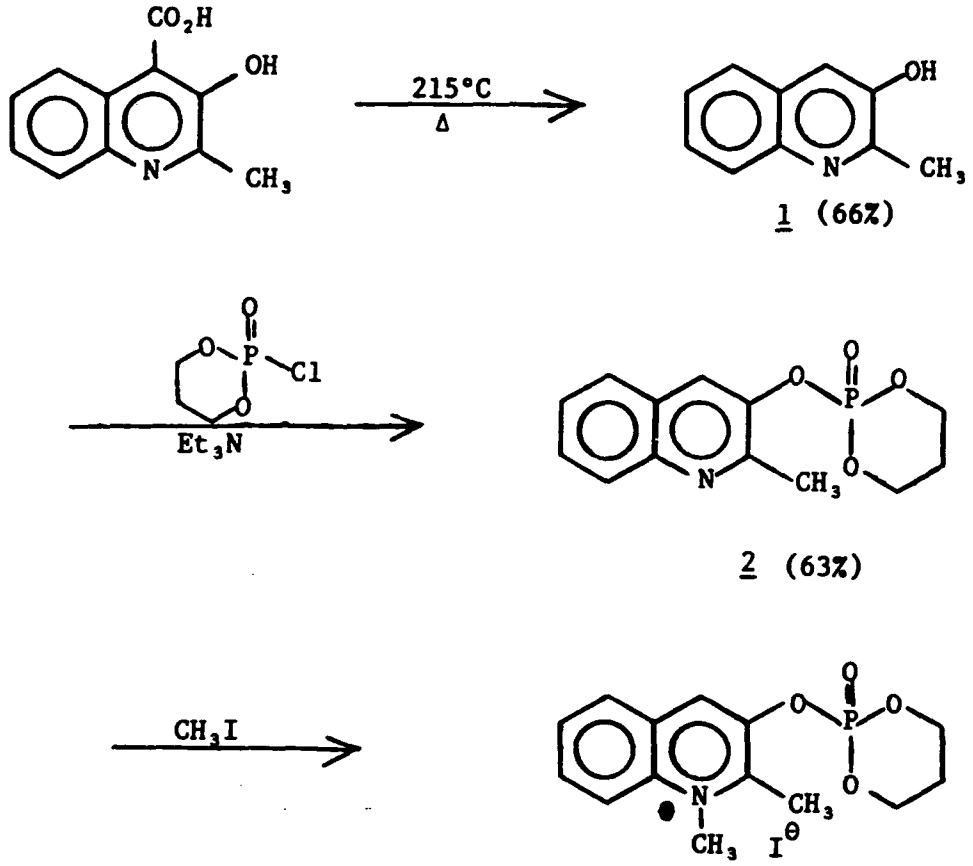
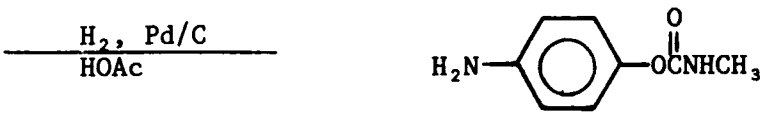


CHART NO. 19

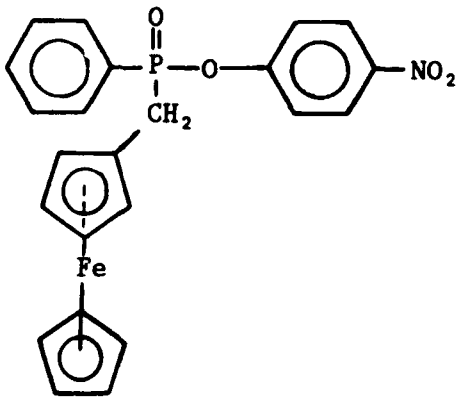
4-AMINOPHENYL N-METHYLCARBAMATE

1 (43%)



2 (32%)

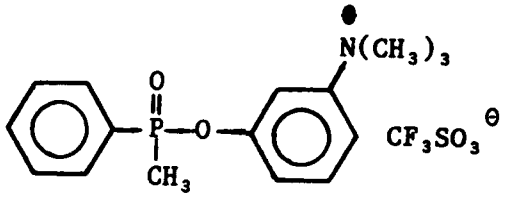
2.27 4-Nitrophenyl ferrocenylmethyl(phenyl)phosphinate



The title compound is a new structure not reported in the chemical literature. The synthesis route developed for the preparation of this compound is shown in Chart No. 20.

The thermal decomposition of trimethylammoniomethyl-ferrocene iodide in excess phenyldimethoxyphosphine gave methyl-phosphinate 1 in 34% yield. Base hydrolysis of phosphinate ester 1 followed by acidification gave phosphinic acid 2 in 68% yield. Intermediate 2 was treated with 4-nitrophenol and dicyclohexyl-carbodiimide to give the title phosphinate ester 3 in 49% yield.

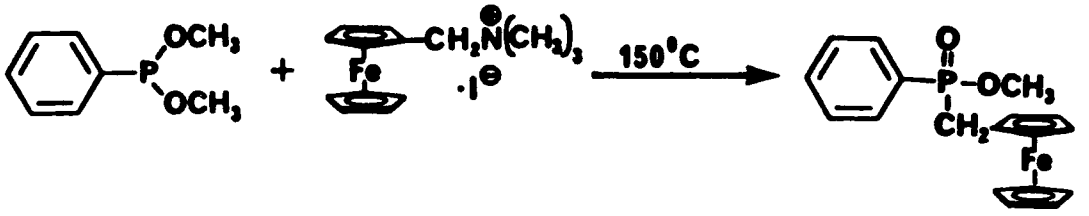
2.28 3-Trimethylammoniophenyl methyl(phenyl)phosphinate trifluoromethylsulfonate



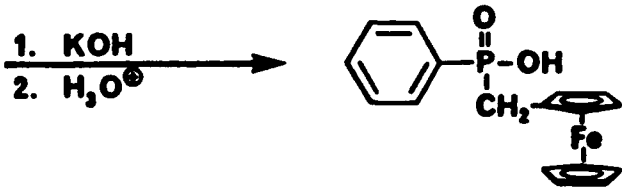
The title compound is the third member of a series of water-soluble phosphinate esters under development by Ash Stevens Inc. in which the water-solubilizing quaternary ammonium substituent is located on the phenolic leaving group. The synthesis route shown in Chart No. 21 parallels that used for the preparation of the corresponding chloromethyl(phenyl) analog (see section 2.7). Methyl(phenyl)phosphinic chloride was coupled with 3-dimethylaminophenol to give the phosphinate ester 1 in 75% yield. Quaternarization of 1 with methyl trifluoromethyl-sulfonate gave the title compound 2 in 70% yield.

CHART NO. 20

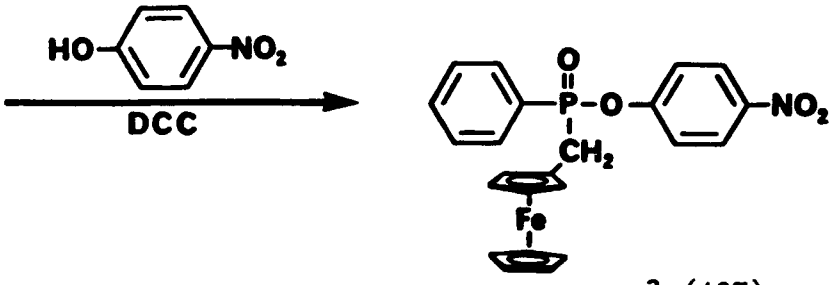
4-NITROPHENYL FERROCENYLMETHYL(PHENYL)PHOSPHINATE



1 (34%)



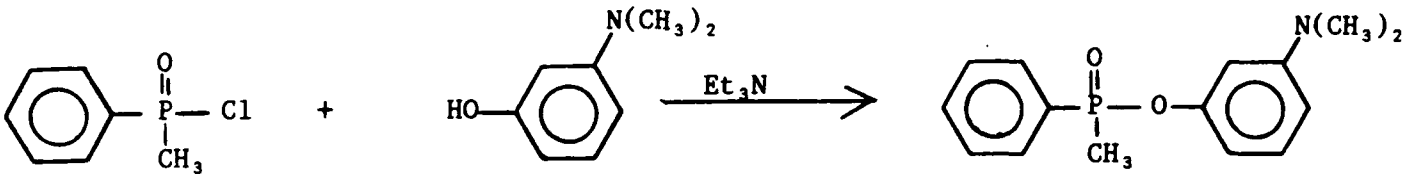
2 (68%)



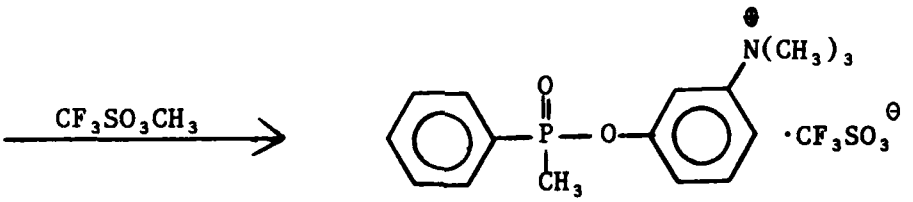
3 (49%)

CHART NO. 21

3-TRIMETHYLAMMONIOPHENYL METHYL(PHENYL)-PHOSPHINATE TRIFLUOROMETHYLSULFONATE

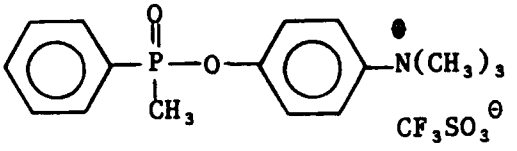


1 (75%)



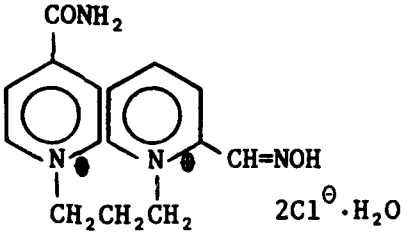
2 (70%)

2.29 4-Trimethylammoniophenyl methyl(phenyl)phosphinate trifluoromethanesulfonate



The title compound is the fourth member of a series of water-soluble phosphinate esters under development by Ash Stevens Inc. in which the water-solubilizing quaternary ammonium substituent is located on the phenolic leaving group. The synthesis route shown in Chart No. 22 parallels that used for the preparation of the corresponding chloromethyl(phenyl) analog (see section 2.5). Methyl(phenyl)phosphinic acid was esterified with 4-dimethylaminophenol in 65% yield using dicyclohexylcarbodiimide as a water acceptor. Treatment of compound 1 with methyl trifluoromethanesulfonate gave the title compound 2 in 91% yield.

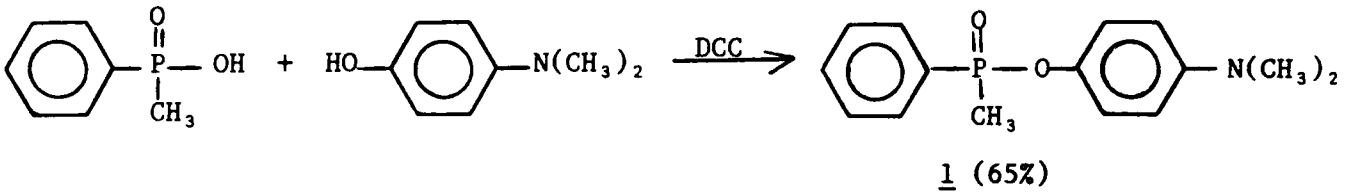
2.30 1-(4-Aminocarbonylpyridinio)-3-(2-hydroxyiminomethyl-pyridinio)propane dichloride monohydrate



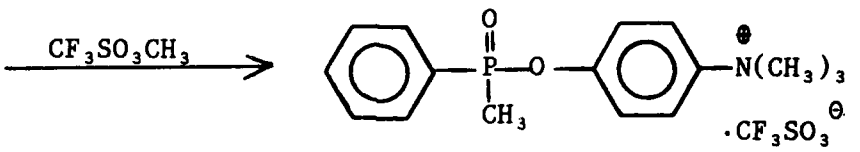
The title compound is a new structure not previously reported in the chemical literature. The three-step synthesis route to the title compound is shown in Chart No. 23. The first two steps of the synthesis sequence follow a procedure supplied by the Project Monitor. Intermediate 1 slowly precipitated from an acetone solution of 2-pyridinealdoxime and 1,3-diodopropane at ambient temperature. After 8 weeks, a 7% yield of quaternary pyridinium iodide 1 was obtained. Heating intermediate 1 with excess isonicotinamide gave the mixed bis-quaternary pyridinium diiodide 2 in 86% yield. Diiodide 2 was converted to the dichloride 3 by passage over Dowex 2-X8 (chloride form) ion exchange resin. Recrystallization from 90% ethanol gave the title compound in 74% yield as a monohydrate.

CHART NO. 22

4-TRIMETHYLAMMONIOPHENYL METHYL(PHENYL)-
PHOSPHINATE TRIFLUOROMETHANESULFONATE



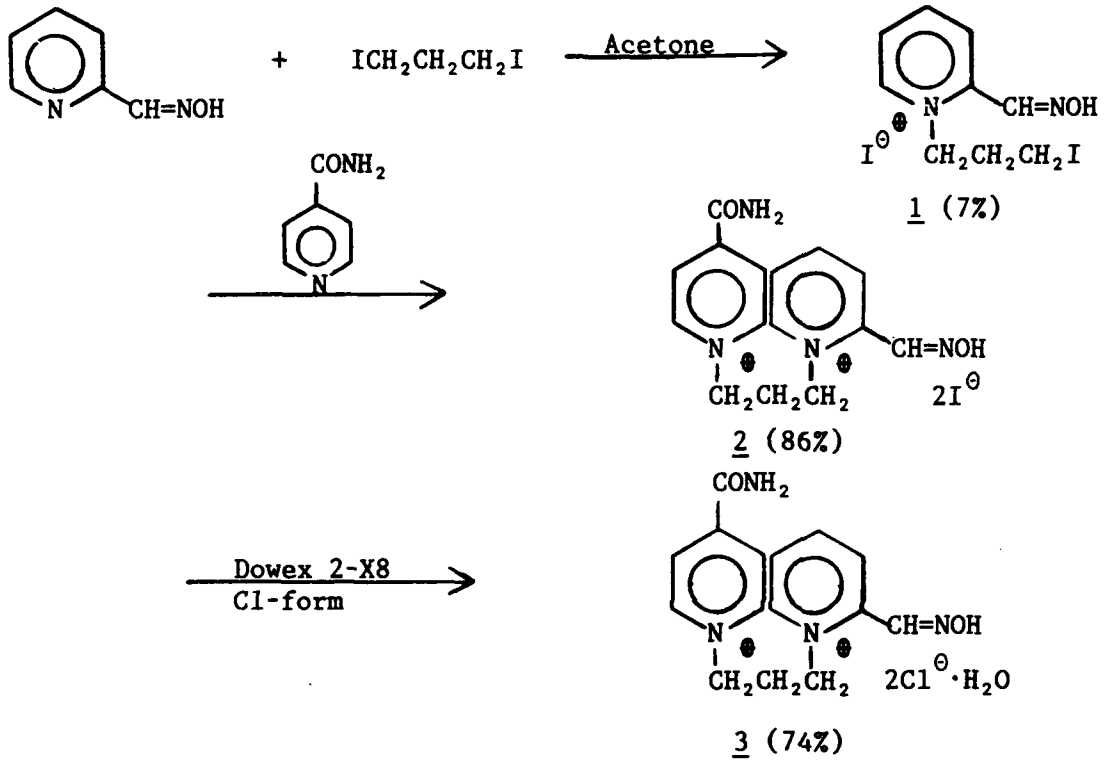
1 (65%)



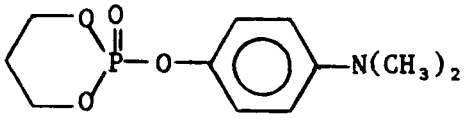
2 (91%)

CHART NO. 23

1-(4-AMINOCARBONYLPYRIDINIO)-3-(2-HYDROXYIMINOMETHYL-PYRIDINIO)PROPANE DICHLORIDE MONOHYDRATE

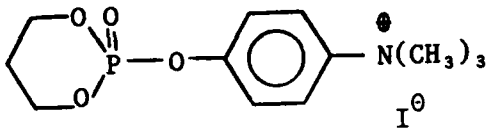


2.31 2-(4-Dimethylaminophenoxy)-2-oxo-1,3,2-dioxaphosphorinane



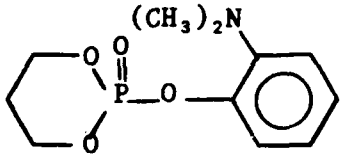
The title compound is a new structure not previously reported in the chemical literature. The synthesis route to the title compound is shown in Chart No. 24. Structure 1 is an intermediate in the preparation of the corresponding 4-trimethylammoniophenyl phosphorate ester 2 which is discussed in section 2.32. Treatment of freshly distilled 4-dimethylaminophenol (10) with 2-chloro-2-oxo-1,3,2-dioxaphosphorinane (12) and triethylamine gave the title compound 1 in 48% yield.

2.32 2-Oxo-2-(4-trimethylammoniophenoxy)-1,3,2-dioxaphosphorinane iodide



The title compound is a new structure not report in the chemical literature. As stated above, the two-step synthesis sequence is shown in Chart No. 24. Compound 2 is a structural isomer of the highly active 2-oxo-2-(3-trimethylammoniophenoxy)-1,3,2-dioxaphosphorinane iodide, first prepared by Ashani, et al. (22). Intermediate 1 was methylated with excess methyl iodide in acetonitrile to give the title compound 2 in 44% yield after recrystallization.

2.33 2-(2-Dimethylaminophenoxy)-2-oxo-1,3,2-dioxaphosphorinane

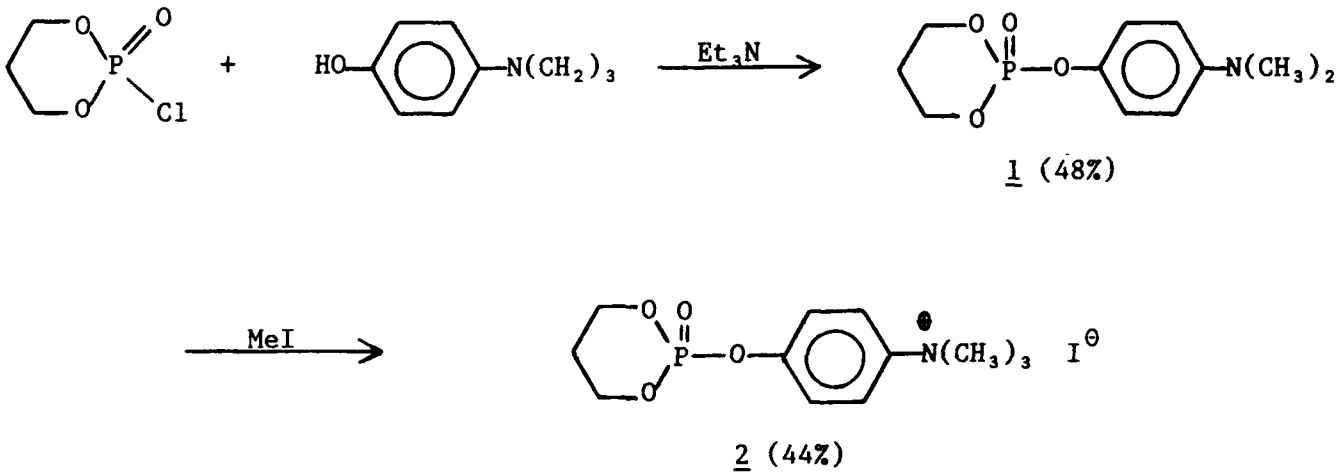


The title compound is a new structure not report in the chemical literature. The three-step synthesis route is shown in Chart No. 25. This compound is an intermediate for the preparation of the corresponding 2-trimethylammoniophenyl phosphorate ester 4 which is discussed in section 2.34.

The dimethylaminophenol (2) was prepared by a two-step procedure. Benzoxazole was methylated with excess methyl iodide to give intermediate 1 in 48% yield.

CHART NO. 24

2-(4-DIMETHYLAMINOPHENOXY)-2-OXO-1,3,2-DIOXAPHOSPHORINANE
AND 2-OXO-2-(4-TRIMETHYLAMMONIOPHENOXY)-1,3,2-DIOXAPHOSPHORINANE IODIDE

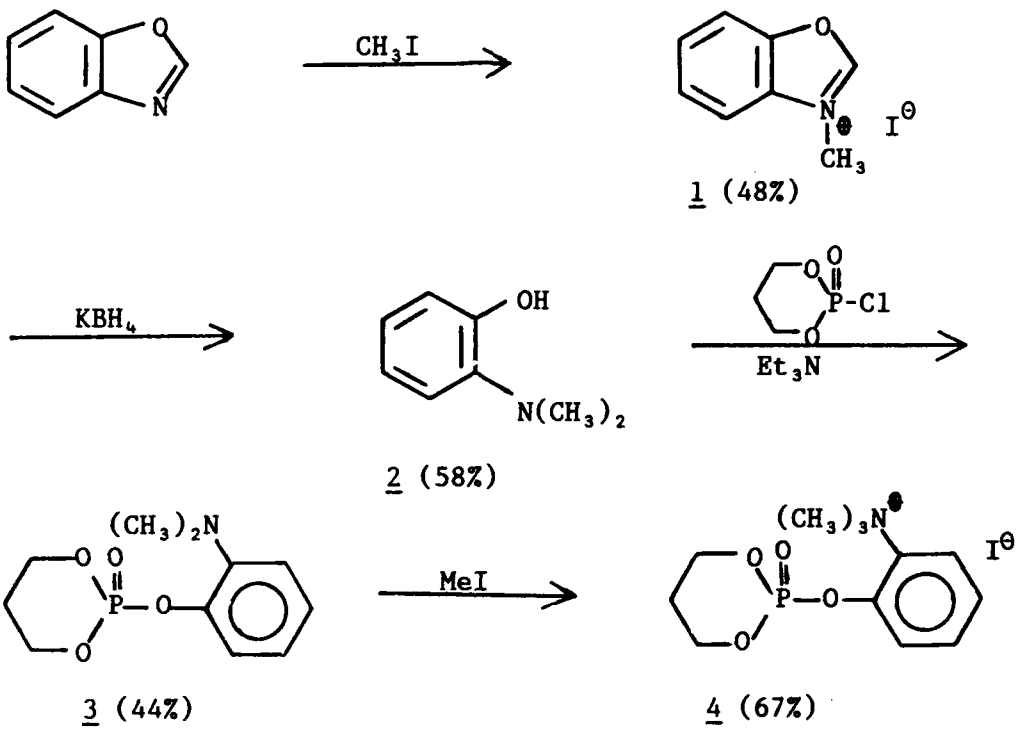


1 (48%)

2 (44%)

CHART NO. 25

2-(2-DIMETHYLAMINOPHENOXY)-2-OXO-1,3,2-DIOXAPHOSPHORINANE AND 2-OXO-2-(2-TRIMETHYLAMMONIOPHENOXY)-1,3,2-DIOXAPHOSPHORINANE IODIDE



1 (48%)

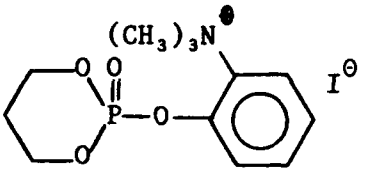
2 (58%)

3 (44%)

4 (67%)

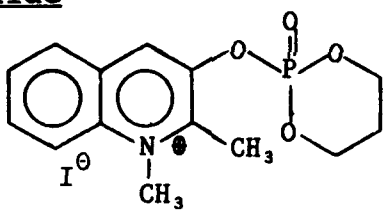
Treatment of benzoxazolium salt 1 with potassium borohydride in water gave 2-dimethylaminophenol (2) in 58% yield after purification by sublimation. Treatment of 2 with 2-chloro-2-oxo-1,3,2-dioxaphosphorinane (12) gave the title phosphorate ester 3 in 44% yield.

2.34 2-Oxo-2-(2-trimethylammoniophenoxy)-1,3,2-dioxaphosphorinane iodide



The title compound is a new structure not reported in the chemical literature. The four-step synthesis route is shown in Chart No. 25. This compound is also a structural isomer of the highly active 2-oxo-2-(3-trimethylammoniophenoxy)-1,3,2-dioxaphosphorinane iodide, first prepared by Ashani et al. (22). Intermediate 3 (section 2.33) was methylated with excess methyl iodide in acetonitrile to give the title compound 4 in 67% yield after purification.

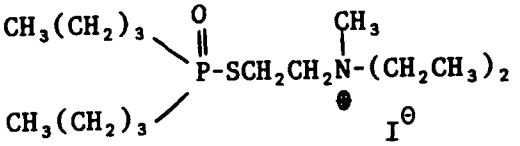
2.35 1,2-Dimethyl-3-(2-oxo-1,3,2-dioxaphosphorinan-2-yloxy)-quinolinium iodide



The synthetic route to this target compound is shown in Chart No. 18.

Phosphorinane ester 2 was prepared as described in section 2.25. Quaternarization of the quinoline nitrogen with methyl iodide in acetonitrile gave the title quaternary quinolinium iodide 3 in 18% yield.

2.36 S-2-N,N-Diethyl-N-methylammonioethyl di(1-butyl)phosphinothioate iodide



The title compound is a new structure not previously reported in the chemical literature. The synthesis route to this target structure is shown in Chart No. 26. Di-1-butylphosphinic acid was prepared by the reaction of diethylphosphite with 1-butyl magnesium chloride followed by oxidation with bromine.

CHART NO. 26

S-2-N,N-DIETHYL-N-METHYLAMMONIOETHYL DI(1-BUTYL)PHOSPHINOTHIOATE IODIDE

$$(CH_3CH_2O)_2P(O)H \xrightarrow[2)\ Br_2]{1)\ BuMgCl} (nC_4H_9)_2P(O)OH$$

1

$$+ \quad PCl_5 \xrightarrow{C_6H_6} (n\text{-}C_4H_9)_2P(O)Cl \quad + \quad P_4S_{10} \xrightarrow{\Delta}$$

2

$$(nC_4H_9)_2P(S)Cl \quad + \quad (CH_3CH_2)_2NCH_2CH_2ONa \xrightarrow{C_6H_6}$$

3

$$(n\text{-}C_4H_9)_2P(O)SCH_2CH_2NEt_2 \quad + \quad CH_3I \xrightarrow{Et_2O}$$

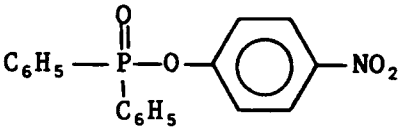
4

$$(CH_3CH_2CH_2CH_2)_2P(O)SCH_2CH_2\overset{\overset{CH_3}{|}}{\underset{}{\overset{\bullet}{N}}}Et_2 \quad I^{\ominus}$$

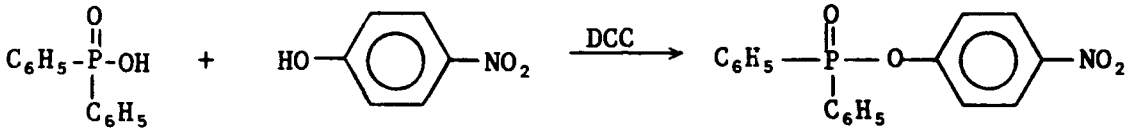
5

Phosphinic acid 1 was converted to the corresponding acid chloride 2 by treatment with phosphorus pentachloride. Treatment of compound 2 with tetraphosphorus decasulfide gave the phosphinothioic acid chloride 3 which was then treated with sodium salt of diethylaminoethanol to give the phosphinothioate 4. The tertiary amino group was quaternarized with methyl iodide to give the title compound 5.

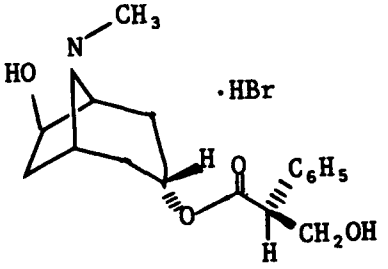
2.37 4-Nitrophenyl diphenylphosphinate



The title compound was prepared earlier by Ash Stevens Inc. under a prior contract (11). For the current resynthesis, the one-step procedure shown below was used. Diphenylphosphinic acid was esterified with p-nitrophenol using dicyclohexylcarbodiimide as a water acceptor to give the title ester in 76% yield.



2.38 (3R,6R)-3,6-Dihydroxytropane 3-(S)(-)-tropate hydrobromide

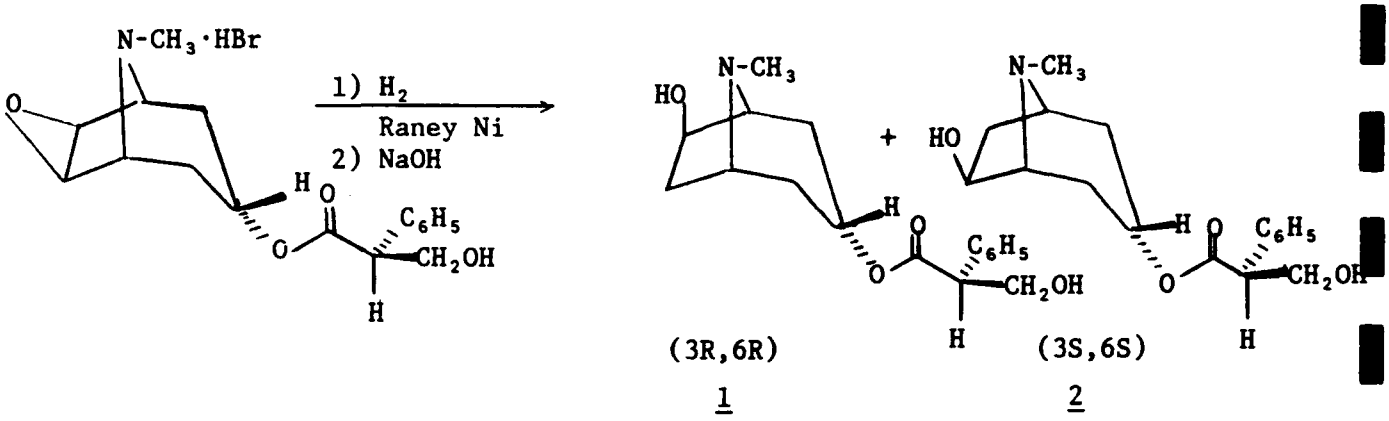


The title compound was prepared by a literature procedure (23) shown in Chart No. 27.

Hydrogenation of scopolamine hydrobromide over neutral Raney nickel catalyst at atmospheric pressure gave a mixture of (3R,6R) and (3S,6S)-3,6-dihydroxytropanes (1 and 2). This mixture of hydrobromide salts was converted to the corresponding free base with dilute sodium hydroxide in 91% yield. Treatment with dibenzoyl-L-tartaric acid gave the tartrates which were separated by fractional crystallization from absolute ethanol to give optically pure (3R,6R)isomer 3. Conversion of intermediate 3 to the title hydrobromide salt was accomplished by passage through an ion-exchange resin column.

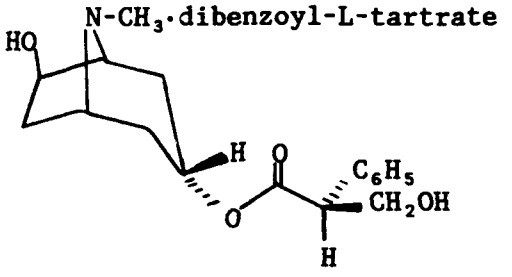
CHART NO. 27

(3R,6R)-3,6-DIHYDROXYTROPANE 3-(S)(-)-TROPATE HYDROBROMIDE



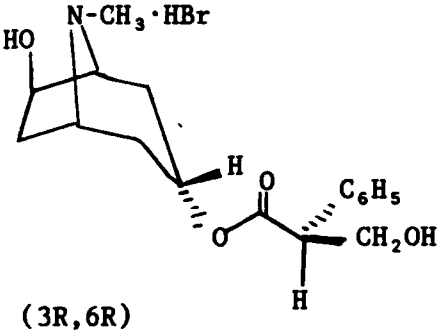
1 2

1) dibenzoyl L-tartaric acid
2) Resolution



3 $[\alpha]_D$ -47.2° (c = 1, CH_3OH)

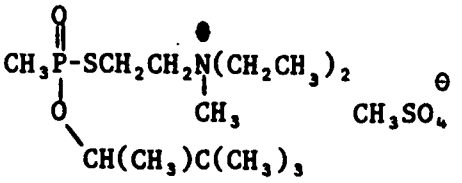
Dowex 2-X8
Br^- form



(3R,6R)

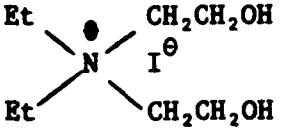
1 $[\alpha]_D$ -10.3° (c = 1, H_2O)

2.39 S-2-N,N-Diethyl-N-methylammonioethyl O-pinacolyl methylphosphonothioate methylsulfate

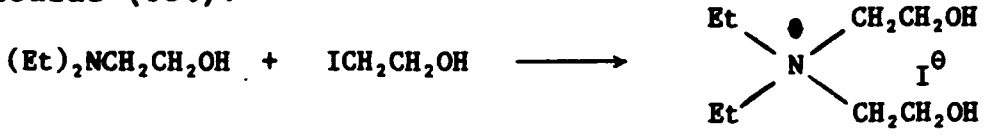


The title compound was prepared as shown in Chart No. 28. Thus, treatment of methylphosphonic dichloride with one equivalent of 3,3-dimethyl-2-butanol and triethylamine gave phosphonate ester 1 (70%). 2-Diethylaminoethanethiol hydrochloride was purified by repeated recrystallization from ethanol, and then it was coupled with intermediate 1 in the presence of a large excess of triethylamine to give the mixed methylphosphonothioate ester 2 (46%). Intermediate 2 was methylated with dimethyl sulfate in acetonitrile to give the title compound in 38% yield after recrystallization.

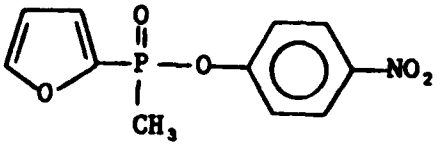
2.40 Diethyldi(2-hydroxyethyl)ammonium iodide



The title compound was prepared by a literature procedure (24) shown below. 2-Diethylaminoethanol was alkylated with 2-iodoethanol in methyl ethyl ketone to give the title amine hydroiodide (85%).



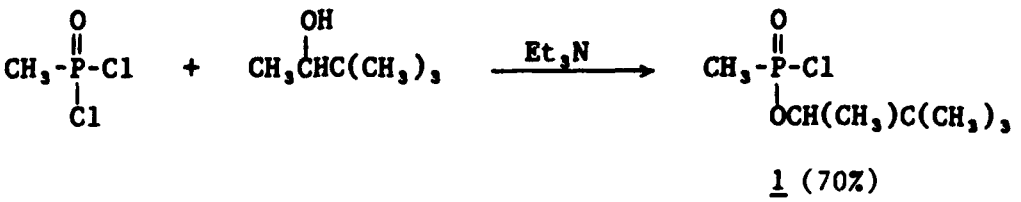
2.41 4-Nitrophenyl 2-furyl(methyl)phosphinate



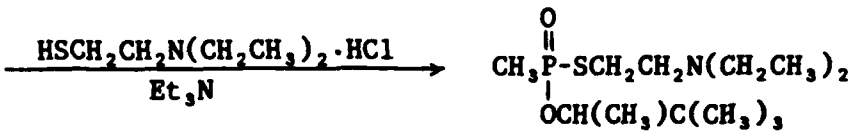
The title compound was prepared earlier by Ash Stevens Inc., under a prior contract (7). For the current resynthesis, the same synthesis sequence shown in Chart No. 29 was used. 2-Furyllithium, prepared *in situ* from furan and n-butyllithium, was treated with phosphorus trichloride to give tris(2-furyl)phosphine (1) in 70% yield. Treatment of compound 1 with methyl iodide gave the quaternary phosphonium iodide 2 (97%). Treatment of compound 2 with sodium hydroxide, in aqueous ethanol at room temperature, gave phosphine oxide 3 (66%). Compound 3 was then

CHART NO. 28

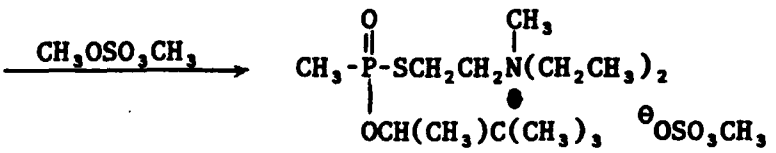
S-2-N,N-DIETHYL-N-METHYLAMMONIOETHYL O-PINACOLYL METHYL PHOSPHONOTHIOATE METHYLSULFATE



1 (70%)



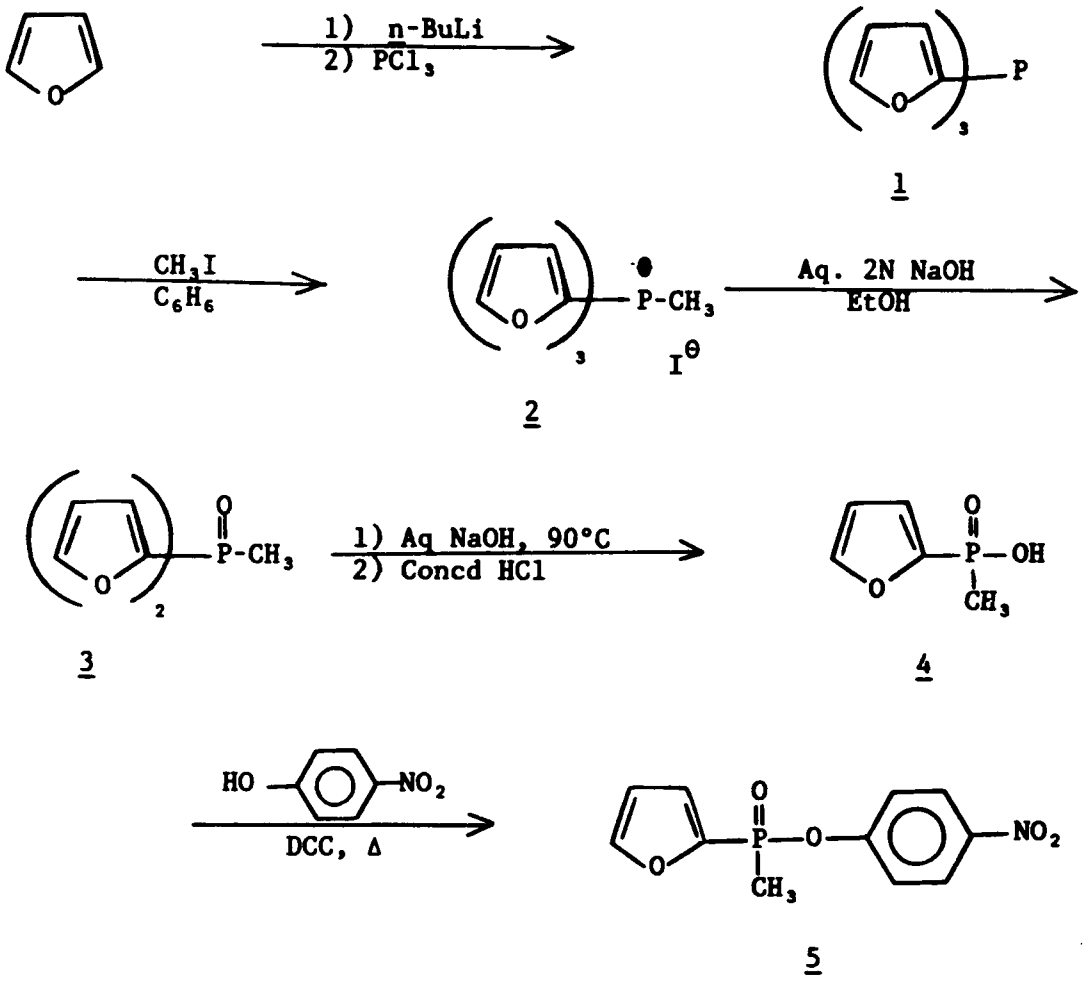
2 (46%)



3 (38%)

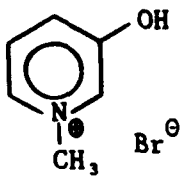
CHART NO. 29

4-NITROPHENYL 2-FURYL(METHYL)PHOSPHINATE

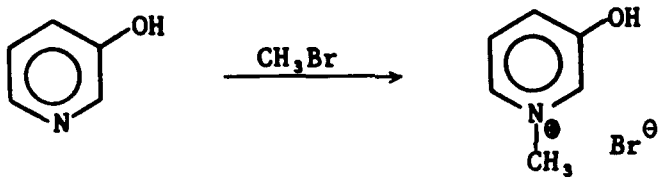


treated with aqueous hydroxide (1 N) at reflux to give phosphinic acid 4 (58%). Esterification of acid 4 with 4-nitrophenol in the presence of dicyclohexylcarbodiimide gave the title target ester 5 in 53% yield. Yields were somewhat lower in four of the five steps. The overall yield was 14% vs. 22.5% in the prior work (7).

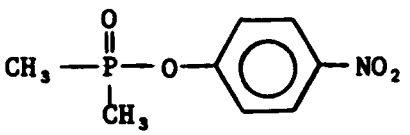
2.42 3-Hydroxy-1-methylpyridinium bromide



The title compound was prepared by a literature procedure (25) shown below. 3-Hydroxypyridine was treated with methyl bromide in acetone to give the title compound in 64% yield after recrystallization.



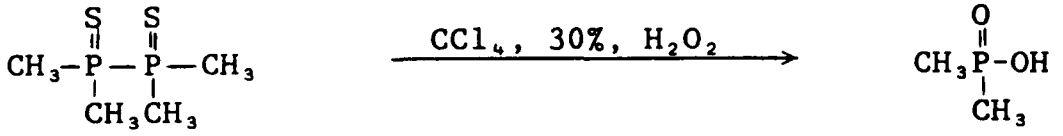
2.43 4-Nitrophenyl dimethylphosphinate



The title compound was prepared earlier by Ash Stevens Inc. under a prior contract (7). For the current resynthesis, the same synthesis sequence shown in Chart No. 30 was used. Tetramethylbiphosphinic disulfide was oxidized with hydrogen peroxide to give dimethylphosphinic acid (1, 81%), which was coupled directly with 4-nitrophenol and dicyclohexylcarbodiimide, and gave the title target ester 2 in 33% yield. The yield in the first step was comparable to that obtained previously (7), in the second step it was 10% lower (7).

CHART NO. 30

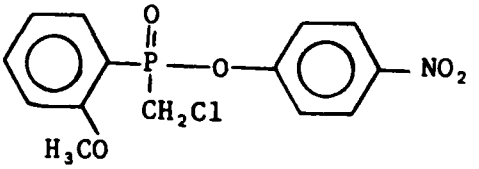
4-NITROPHENYL DIMETHYLPHOSPHINATE



1 (81%)

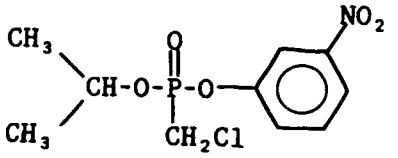
2 (33%)

2.44 4-Nitrophenyl chloromethyl(2-methoxyphenyl)phosphinate



The title compound was prepared earlier by Ash Stevens Inc., under a prior contract (11). The current resynthesis utilized the same synthesis sequence shown in Chart No. 31. Phosphorus trichloride was treated with diethylamine to give intermediate 1 in 81% yield. Treatment of intermediate 1 with 2-methoxyphenylmagnesium bromide gave the phosphonous diamide 2 in 64% yield. Conversion of the phosphonous diamide 2 to the required phosphonous dichloride 3 was accomplished with anhydrous hydrogen chloride in ether to give the compound in 74% yield. Treatment of intermediate 3 with 1.5 equivalents of paraformaldehyde gave chloromethylphosphinic chloride 4 (52%); this was esterified with 4-nitrophenol in the presence of diisopropylethylamine to give the title compound 5 in 17% yield. Product yields for the first four steps were comparable or slightly higher to those reported previously (11). Yield in the last step was considerably lower. This may be due to partial hydrolysis of the product during workup.

2.45 3-Nitrophenyl 2-propyl chloromethylphosphonate



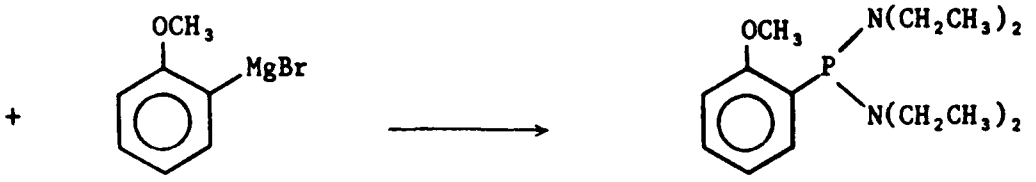
The title diester of chloromethylphosphonic acid has not been reported in the chemical literature. The synthetic route, shown in Chart No. 32, is similar to that used in these laboratories to prepare analogous mixed diesters of methylphosphonic acid.

Thus, chloromethylphosphonic dichloride was treated with m-nitrophenol and triethylamine in tetrahydrofuran as solvent to give the bis(m-nitrophenyl) ester 1 (85%). Compound 1 was treated with cold, dilute base to give chloromethylphosphonic acid monoester 2 (50%). Finally, esterification of acid 2 with isopropanol and dicyclohexylcarbodiimide gave the title mixed diester 3 (47%).

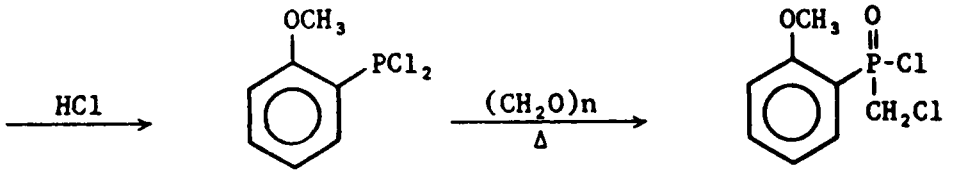
CHART NO. 31

4-NITROPHENYL CHLOROMETHYL(2-METHOXYPHENYL)PHOSPHINATE

1 (81%)

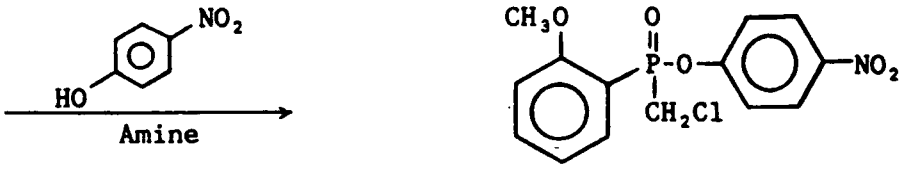


2 (64%)



3 (74%)

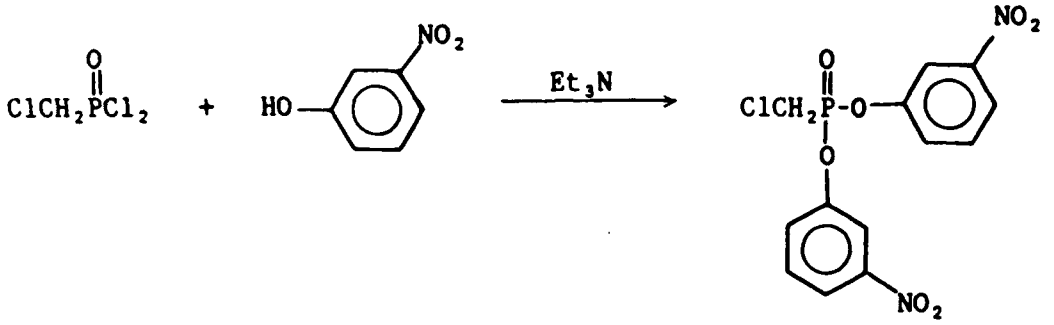
4 (52%)



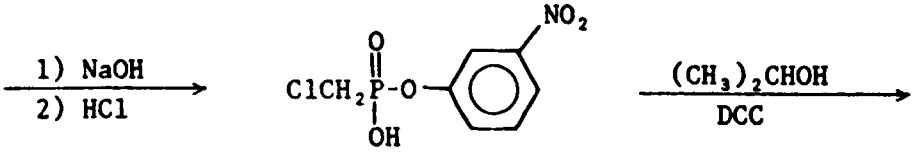
5 (17%)

CHART NO. 32

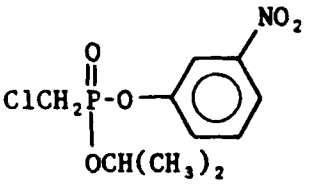
3-NITROPHENYL 2-PROPYL CHLOROMETHYLPHOSPHONATE



1 (85%)

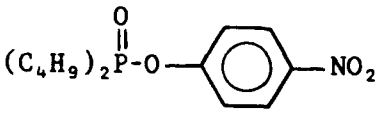


2 (50%)



3 (47%)

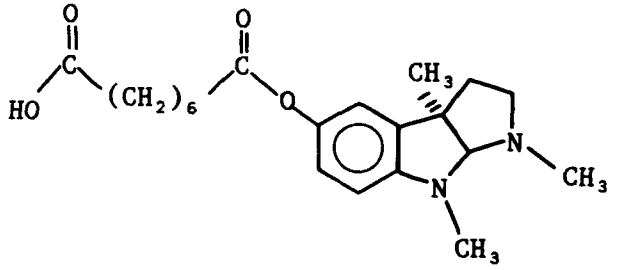
2.46 4-Nitrophenyl dibutylphosphinate



A sample of the title compound was prepared earlier by Ash Stevens Inc. under a prior contract (9). The same sequence shown in Chart No. 33 was used for two current resyntheses, 8 g (8/87) and 25 g (1/88).

Diethyl phosphite was treated with three equivalents of n-butylmagnesium bromide, and the product was oxidized with bromine according to a literature procedure (26) to give dibutylphosphinic acid (1). The acid 1 was converted to phosphinic chloride 2 by treatment with phosphorus pentachloride. Chloride 2 was allowed to react with 4-nitrophenol and triethylamine to give the title compound 3 which was purified by column chromatography over acidic alumina. The yield of purified ester 3 depends in part on the quality of alumina used in the purification step. One batch of alumina used in the current work was not sufficiently acidic and caused considerable product decomposition.

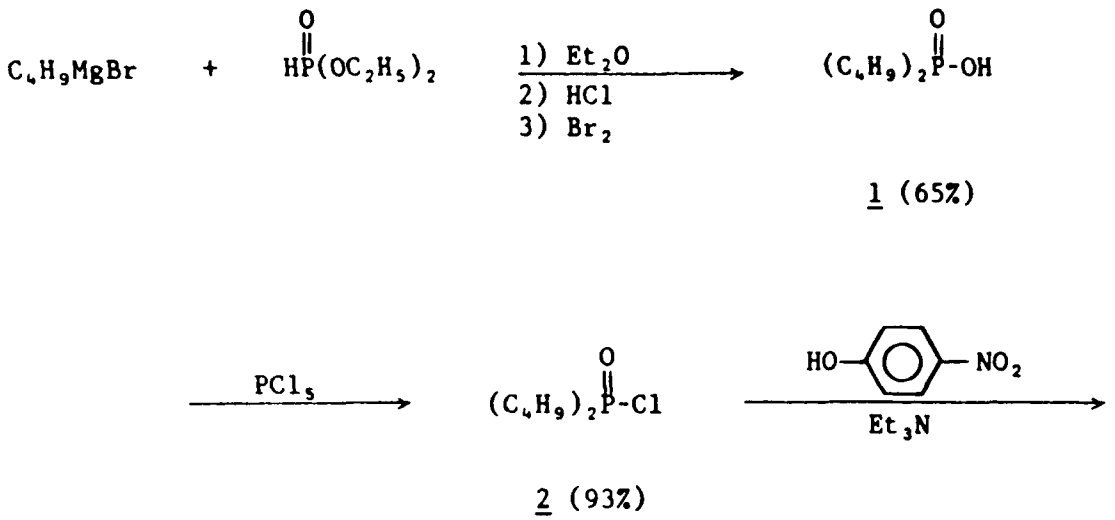
2.47 1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrollo-[2,3-b]indol-5-ol (7-carboxy)heptanoate ester

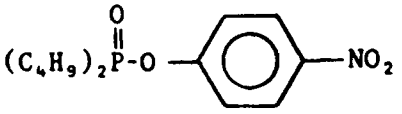


The title ester, a physostigmine analog, is a new structure not previously reported in the chemical literature. The synthesis route, starting with physostigmine, is shown in Chart No. 34. Thus, physostigmine was hydrolyzed with concentrated hydrochloric acid, and the product was treated with bicarbonate to give the substituted indole 1 (eseroline). Treatment of compound 1 with suberoyl chloride did not give the desired 5-O-ester, but led instead to N-acylation of the outside ring nitrogen with concomitant ring opening and formation of a nitrogen-to-carbon double bond in the five-membered indole ring. The coupling of compound 1 with monobenzyl suberate in the presence of dicyclohexylcarbodiimide did proceed satisfactorily, however, to give ester 2. Finally, hydrogenolysis of the benzyl group with palladium and 1,4-cyclohexadiene gave the desired title target structure 3.

CHART NO. 33

4-NITROPHENYL DIBUTYLPHOSPHINATE

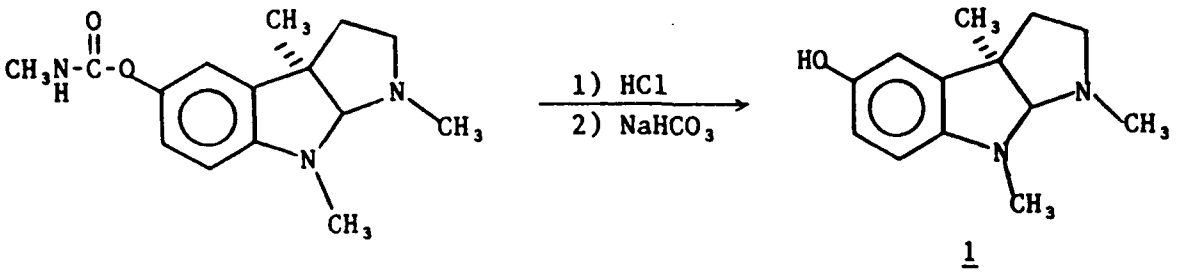




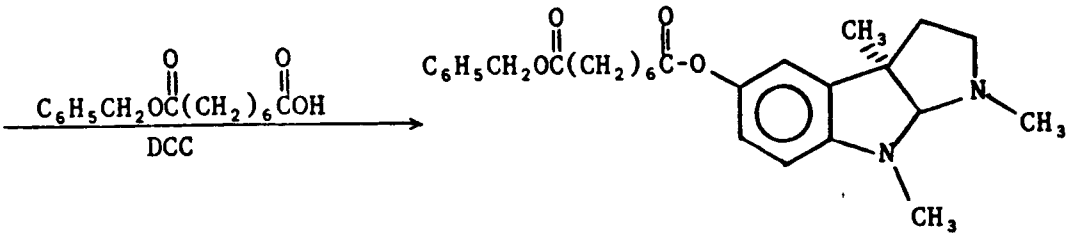
3 (65%)

CHART NO. 34

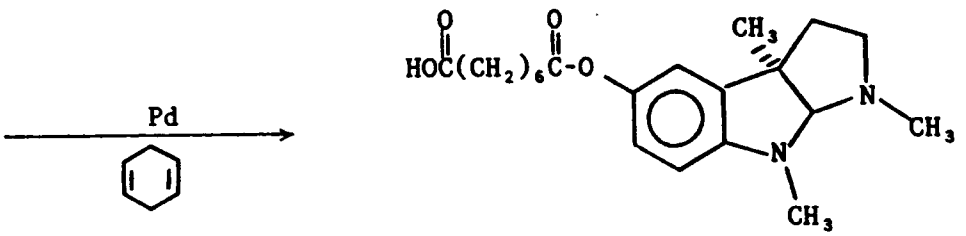
1,2,3,3a,8,8a-HEXAHYDRO-1,3a,8-TRIMETHYLPYROLLO-[2,3-b]INDOL-5-OL (7-CARBOXY)HEPTANOATE ESTER



1



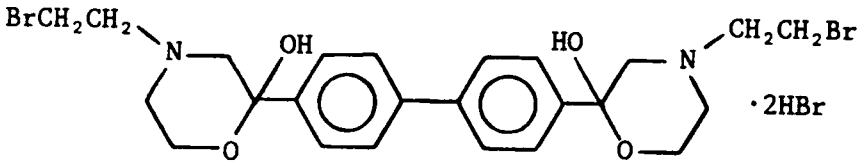
2



2.48 5-Nonanone

The title compound was prepared by the reaction of 5-nonanone with hydroxylamine in aqueous ethanol. The crude product was purified by distillation to give the pure oxime (70%), a mobile oil.

2.49 2,2'-(4,4'-Biphenylene)bis[2-hydroxy-4-(2-bromoethyl)-morpholine] dihydrobromide



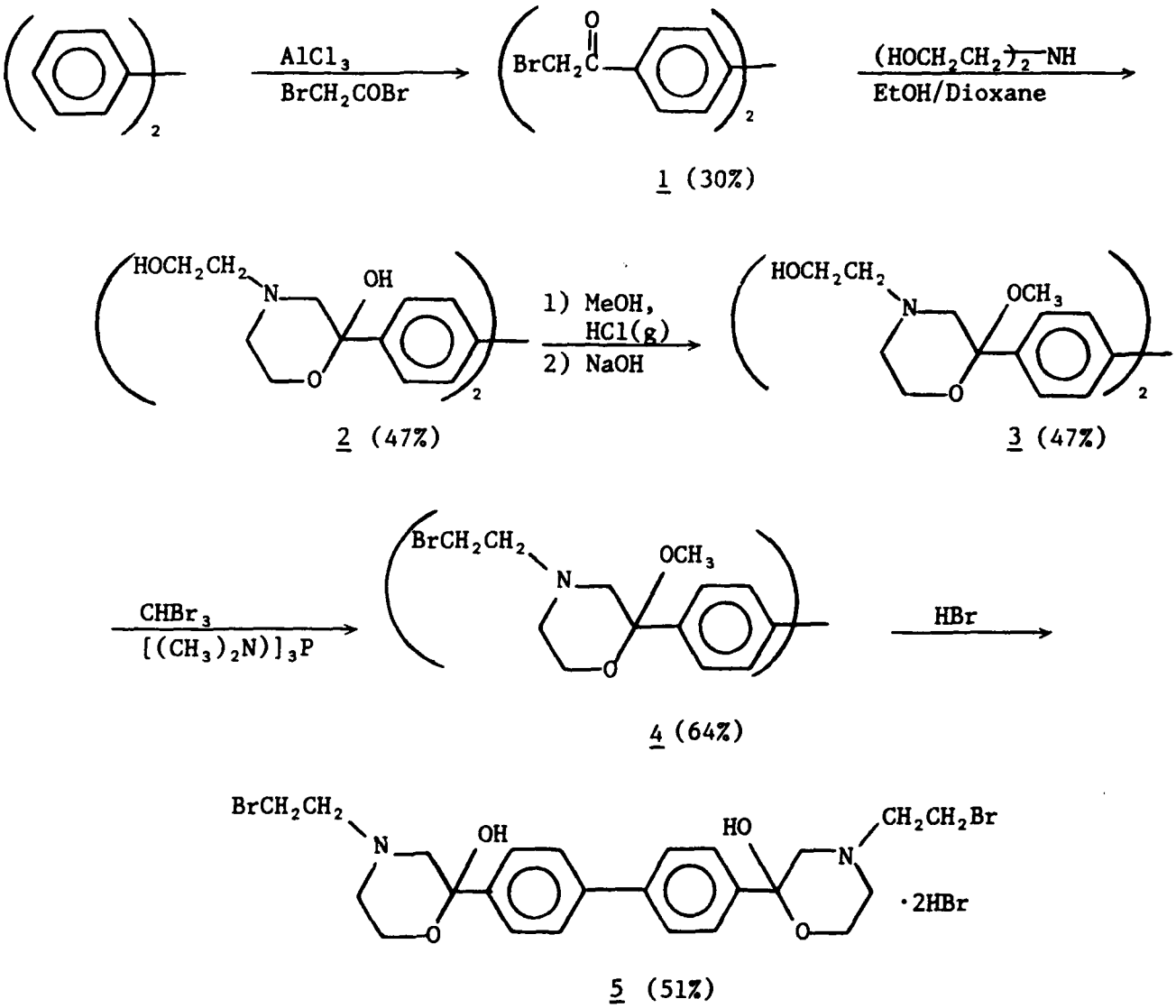
Synthesis of the title compound by a five-step reaction sequence has been reported in the literature (27). The same general sequence, shown in Chart No. 35, was used for the current synthesis.

Condensation of α-bromoacetyl bromide with biphenyl in the presence of anhydrous aluminum chloride gave the bromoketone 1, isolated in two crops in 30% combined yield. Although the compound had a somewhat lower melting point than that reported (27), it was sufficiently pure for use in the next step. Treatment of intermediate 1 with excess diethanolamine in ethanol/dioxane as solvent gave the bis(hydroxymorpholine) 2 in 47% yield. Next, the literature reported the reaction of compound 2 with ethanol and hydrogen chloride to give a 36% yield of the 2-ethoxy analog of compound 3. Although this procedure was repeated successfully in these laboratories on small-scale runs, excessively large solvent volumes were required and product yields were not reproducible from one run to the next. Accordingly, the procedure was modified in that methanol was substituted for ethanol as the solvent. This allowed a five fold reduction in the reaction volume and gave the bis(2-methoxy-morpholine) 3 in 47% yield.

Substitution of the primary hydroxyl group with a bromine was accomplished by treatment of compound 3 with tris(dimethyl-amino)phosphine and bromoform. The literature (27) reported methylene chloride as the reaction solvent. In our study, when methylene chloride was used as the solvent, the isolated product 4 was shown to contain 5-15% of the corresponding chloroethyl

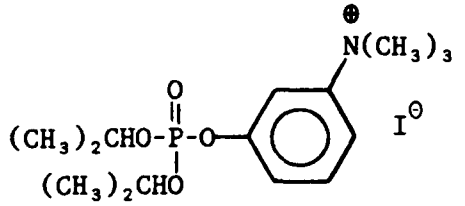
CHART NO. 35

2,2'-(4,4'-BIPHENYLENE)BIS[2-HYDROXY-4-(2-BROMOETHYL)-MORPHOLINE] DIHYDROBROMIDE



compound as an impurity. All attempts to remove this contaminant were unsuccessful. The problem was readily solved, however, by replacing methylene chloride with methylene bromide to give pure intermediate 4 in 64% yield. In the final step, the morpholine 2-ethoxy group was cleaved with acid to yield the title target compound 5. The literature work employed sulfuric acid for this hydrolysis. The crude product was then converted, via the free base, to a hydrochloride salt which was isolated in 27% yield. In the present study, the hydrolysis was accomplished with hydrobromic acid, and product 5 was isolated as a hydrobromide salt in 51% yield. By this procedure, conversion of compound 5 to the free base was not necessary; this avoided any potential hydrolysis (or halogen exchange) of the reactive bromoethyl nitrogen mustard.

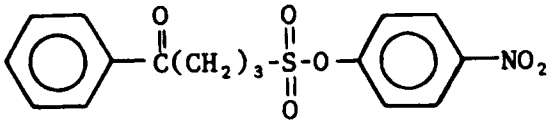
2.50 3-(Diisopropylphosphato)phenyltrimethylammonium iodide



Synthesis of the title compound, methylsulfate salt, has been reported in the literature (28). The same general synthesis sequence, shown in Chart No. 36, was used for the current synthesis.

Diisopropyl phosphorochloridate was prepared by the action of sulfuryl chloride on diisopropyl phosphite, which, in turn, was prepared in situ from phosphorus trichloride and isopropanol. Treatment of chloridate 1 with 3-dimethylaminophenol gave the mixed phosphate triester 2. Purification of ester 2 has been reported (28) by distillation under high vacuum (10^{-6} mmHg). In the present work, the crude product 2 traveled as a single spot on thin-layer chromatography; accordingly, the compound was used as such, without purification, in the next step. Treatment of crude 2 with methyl iodide in acetonitrile as solvent gave the title quaternary iodide salt.

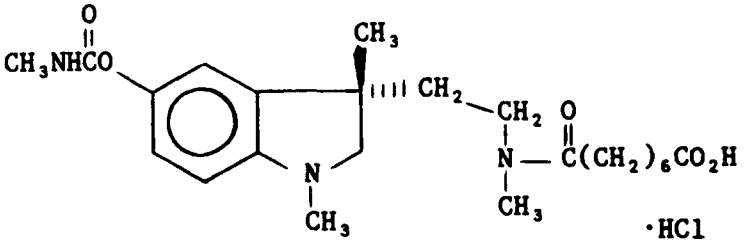
2.51 4-Nitrophenyl 3-(benzoyl)propanesulfonate



The title compound represents a new structure not reported in the chemical literature. The four-step synthesis route is shown in Chart No. 37.

Bromoketone 1 was prepared by the Friedel-Crafts acylation of benzene with bromopropionyl chloride as described in the literature (29). Treatment of compound 1 with sodium sulfite in aqueous ethanol as solvent gave the sulfonic acid sodium salt 2. In the initial studies, a sample of 2 was passed over a strong acid ion exchange resin to give the free sulfonic acid in the form of an oil, which rapidly darkened on standing. As a result, the stable sodium salt was used in all subsequent work. Treatment of compound 2 with a mixture of thionyl chloride and dimethylformamide gave a low yield of the desired sulfonyl chloride 3. Attempts to convert 2 to 3 using phosphorus pentachloride failed altogether. Thin-layer chromatography (TLC) showed only decomposition products; none of the acid chloride could be detected. Last, the reaction of compound 3 with 4-nitrophenol in the presence of triethylamine gave a high yield of the desired title target structure 4.

2.52 1,3-Dimethyl-3-[2-[N-methyl-N-(7-carboxyheptanoyl)]amino-ethyl]-5-(N-methylcarbamoyloxy)-2,3-dihydroindole hydrochloride



The synthesis route to the title compound is outlined in Chart No. 38 and is based on earlier work reported in the literature (30), which showed that reduction of eserethole, a close analog of physostigmine, with zinc and hydrochloric acid or catalytic hydrogenation in the presence of acetic acid cleaves the fused outside pyrrolle ring of the three-ring system. In the present study with physostigmine, the conditions were changed such that the acetic or hydrochloric acid was replaced with an acid chloride, and sodium borohydride was used as the reducing agent.

CHART NO. 36

3-(DIISOPROPYLPHOSPHATO)PHENYLTRIMETHYLAMMONIUM IODIDE

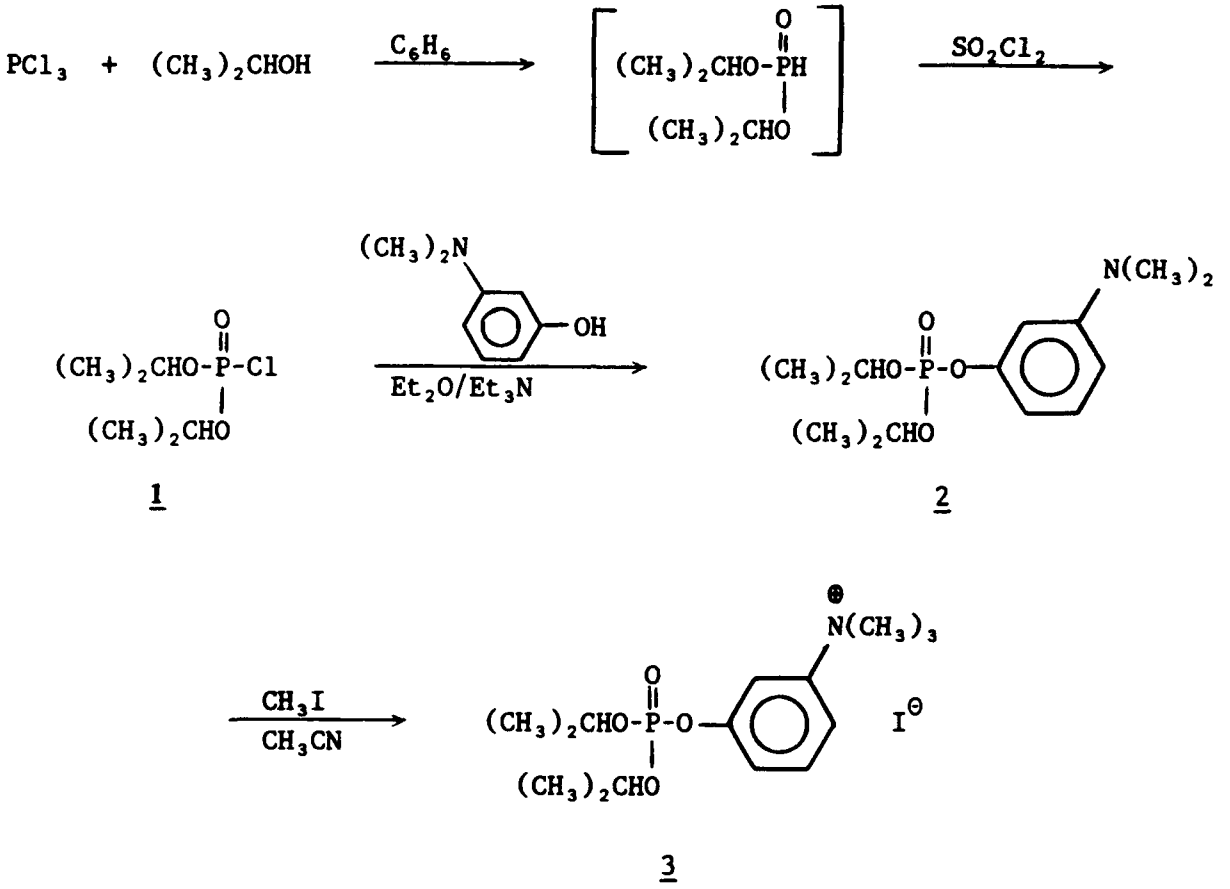
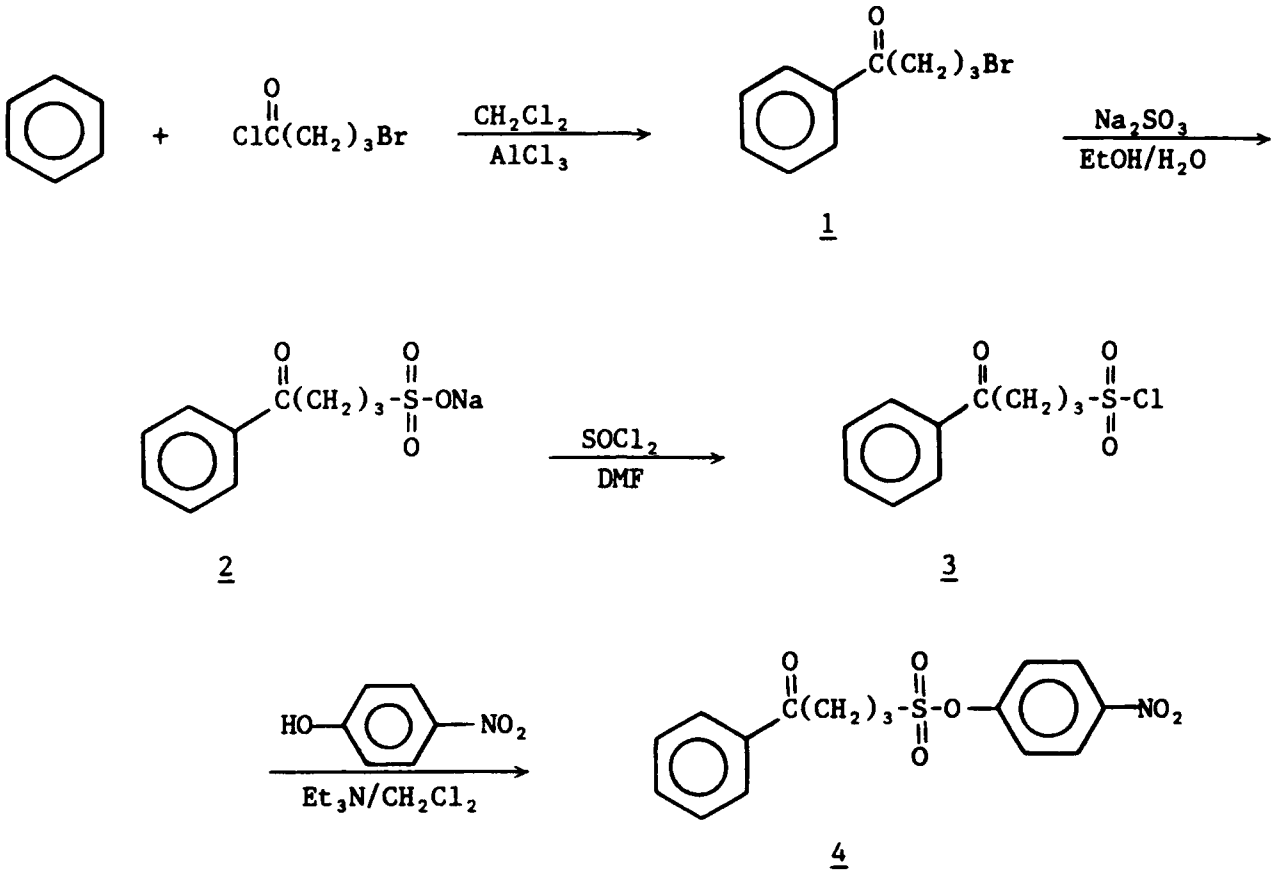


CHART NO. 37

4-NITROPHENYL 3-(BENZOYL)PROPANESULFONATE



1

2

3

4

CHART NO. 38

1,3-DIMETHYL-3-[2-[N-METHYL-N-(7-CARBOXYHEPTANOYL)]-AMINOETHYL]-5-(N-METHYLCARBAMOYLOXY)-2,3-DIHYDRO-INDOLE HYDROCHLORIDE

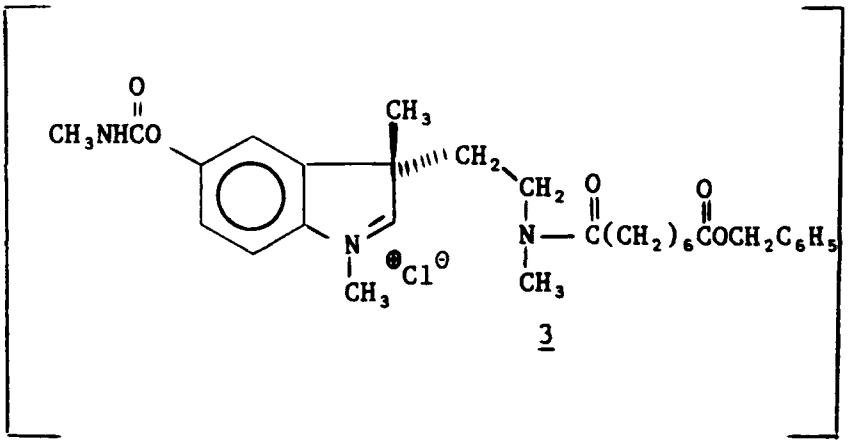
$ClCO(CH_2)_6COCl$ —(1) $C_6H_5CH_2OH$, Et_3N; (2) H_2O→ $C_6H_5CH_2OCO(CH_2)_6CO_2H$

1 (26%)

1 + $SOCl_2$ → $C_6H_5CH_2OCO(CH_2)_6COCl$

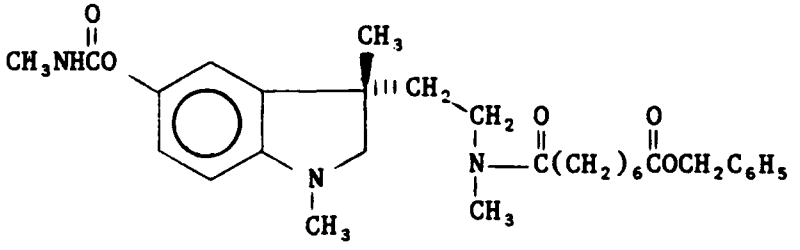
2

2 + Physostigmine →



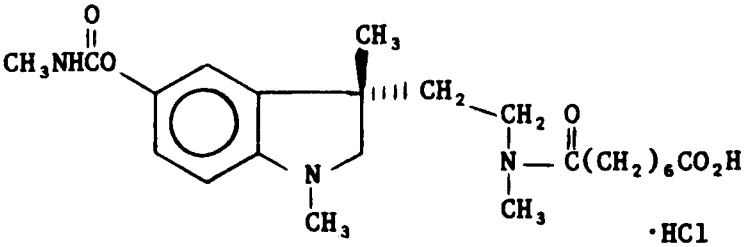
3

$NaBH_4$ →



4 (73%)

1) H_2/Pd; 2) HCl (g) →

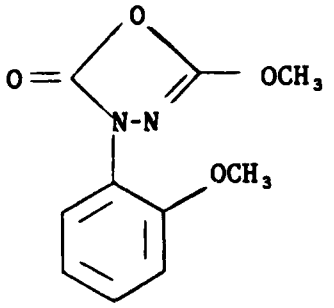


·HCl

5 (85%)

The requisite acid chloride was prepared, as shown, by treating suberoyl chloride with 1 mol of benzyl alcohol; this was followed by hydrolysis to give suberic acid monobenzyl ester 1. After removing some unreacted suberic acid and the dibenzyl ester, compound 1 was converted to acid chloride 2 with thionyl chloride. Next, the acid chloride was treated with physostigmine to give the presumed intermediate 3, which was reduced immediately with sodium borohydride to the substituted indole 4. The crude product was purified by column chromatography, then subjected to hydrogenolysis over palladium black to give compound 5, isolated as a hydrochloride salt. The structure of product 5 was confirmed by infrared and nuclear magnetic resonance (NMR) spectra and elemental analysis.

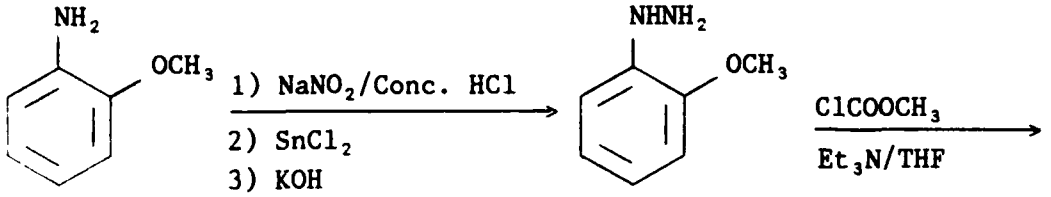
2.53 5-Methoxy-3-(2-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-one



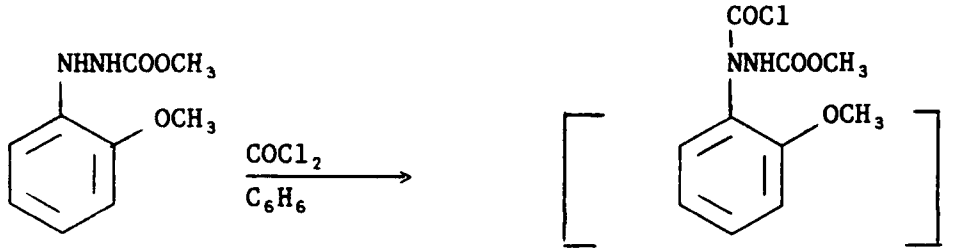
The title compound was prepared by a literature procedure (31,32) and is outlined in Chart No. 39. The required starting material, (2-methoxyphenyl)hydrazine (1), was prepared from o-anisidine by a standard reaction sequence involving diazotization followed by reduction with tin chloride. Treatment of compound 1 with methyl chloroformate gave the carbazate 2. Next, a benzene solution of 2 was treated with phosgene to give the chloro-carbonyl carbazate 3. In the literature procedure (32), this intermediate was isolated, then cyclized with sodium hydroxide to the desired product 4. In the current work, isolation of compound 3 was omitted. Instead, the reaction mixture containing crude 3 was treated directly with methanol and diisopropyl-ethylamine to give the desired title compound. The yield for the two steps, although somewhat lower than the yield in the literature, was quite acceptable.

CHART NO. 39

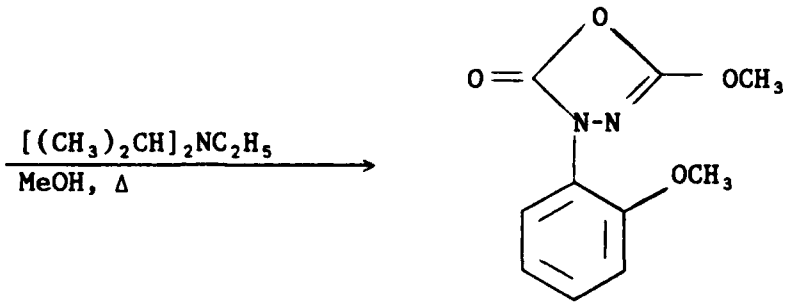
5-METHOXY-3-(2-METHOXYPHENYL)-1,3,4-OXADIAZOL-2(3H)-ONE



1 (71%)

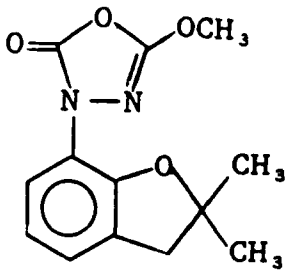


2 (88%) 3



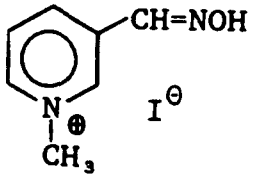
4 (68% from 2)

2.54 3-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-5-methoxy-1,3,4-oxadiazol-2(3H)-one



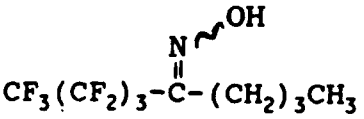
The title compound was prepared by a general literature procedure (33,34), as outlined in Chart No. 40. 2-Nitrophenol was treated with methallyl chloride in the presence of base to give the ether 1, which rearranged at 185-250°C to yield the disubstituted phenol 2. Acid-catalyzed cyclization of compound 2 to 7-nitrobenzofuran 3, followed by catalytic hydrogenation, gave 7-aminobenzofuran 4. Compound 4 was converted to the hydrazine 5 by a standard diazotization reduction sequence. Intermediate 5 was treated with methyl chloroformate in the presence of diisopropylethylamine to give crystalline intermediate 6. Finally, reaction of compound 6 with phosgene gave the N-chlorocarbonyl derivative 7 which was not isolated, but it was treated directly with methanol and diisopropylethylamine to give the title target compound 8. With the exception of intermediate 2, the yields throughout the sequence were good. No comparison could be made with the literature, since no yields were reported.

2.55 3-Pyridinealdoxime methiodide



The title compound was prepared by the quaternarization of commercially available 3-pyridinealdoxime with methyl iodide. One recrystallization gave analytically pure title compound.

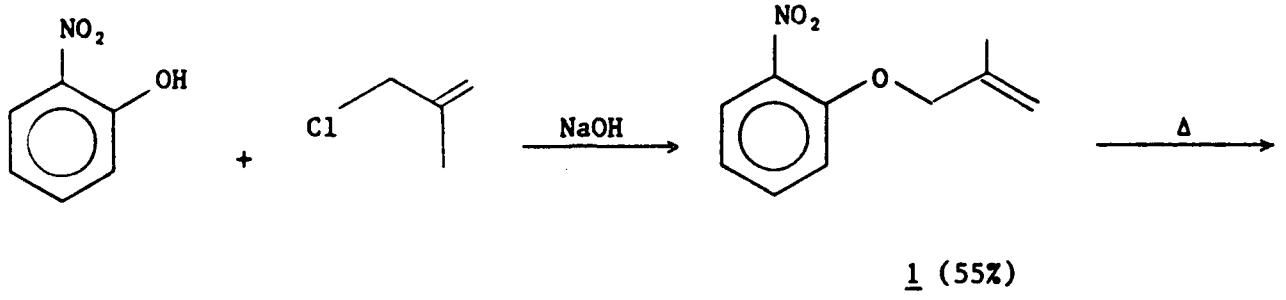
2.56 [1-(Nonafluorobutyl)pentylidene]hydroxylamine



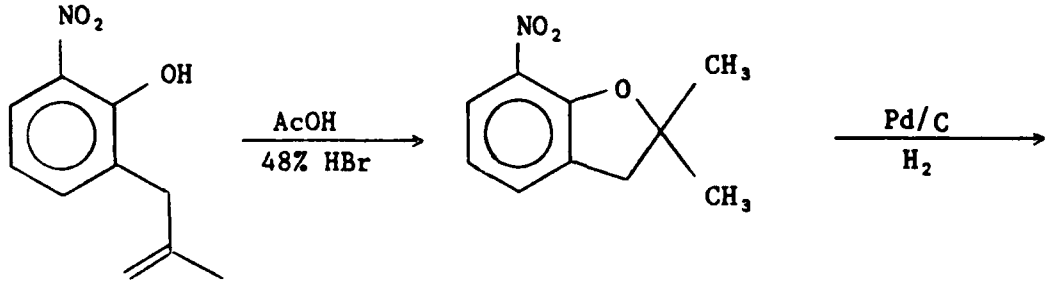
The title structure is a new compound not reported in the chemical literature. Synthesis of this target was accomplished as shown in Chart No. 41. Alcohol 1 was prepared following a

CHART NO. 40

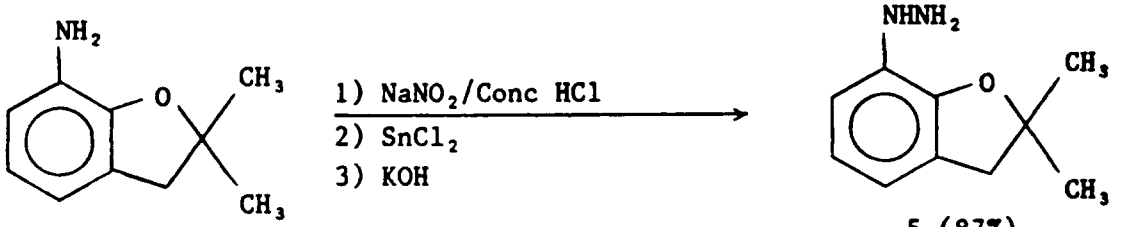
3-(2,3-DIHYDRO-2,2-DIMETHYLBENZOFURAN-7-YL)-5-METHOXY-1,3,4-OXADIAZOL-2(3H)ONE



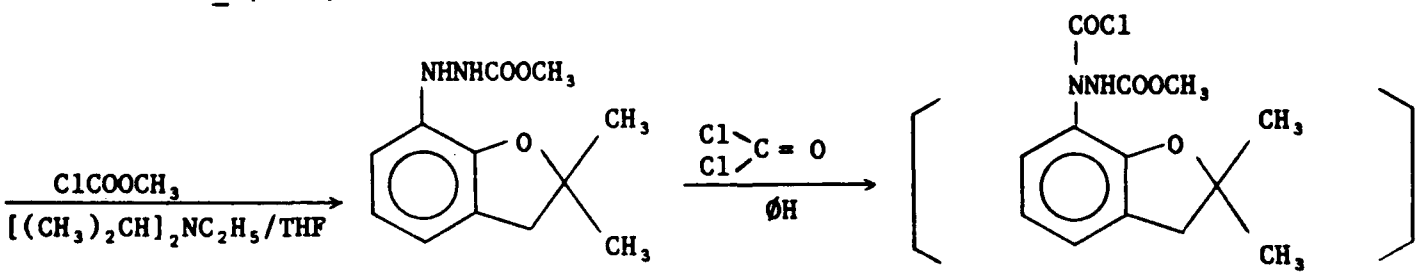
1 (55%)



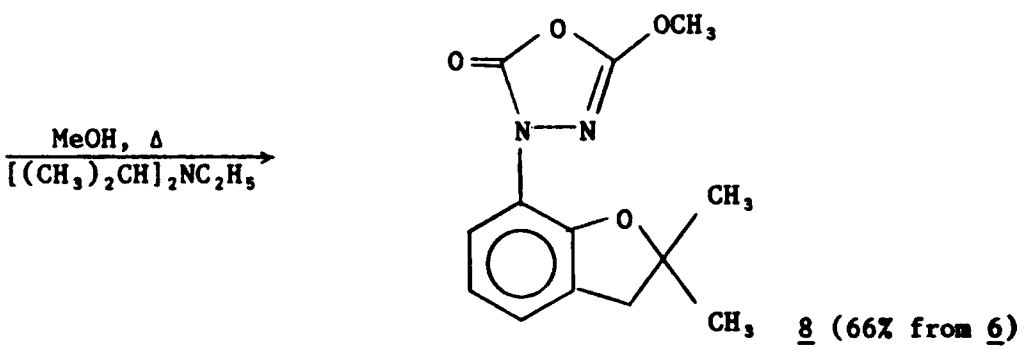
2 (48%) 3 (76%)



4 (100%) 5 (87%)



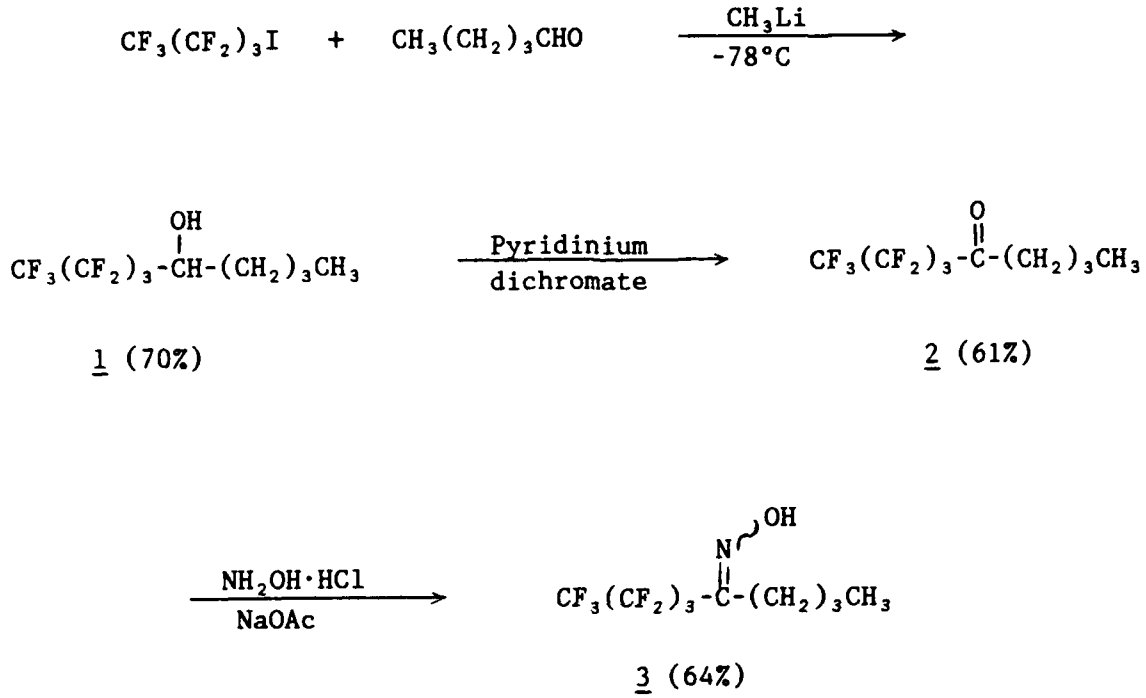
6 (74%) 7



8 (66% from 6)

CHART NO. 41

[1-(NONAFLUOROBUTYL)PENTYLIDENE]HYDROXYLAMINE



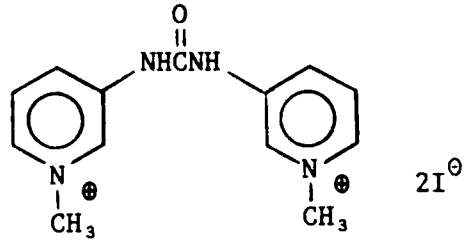
1 (70%)

2 (61%)

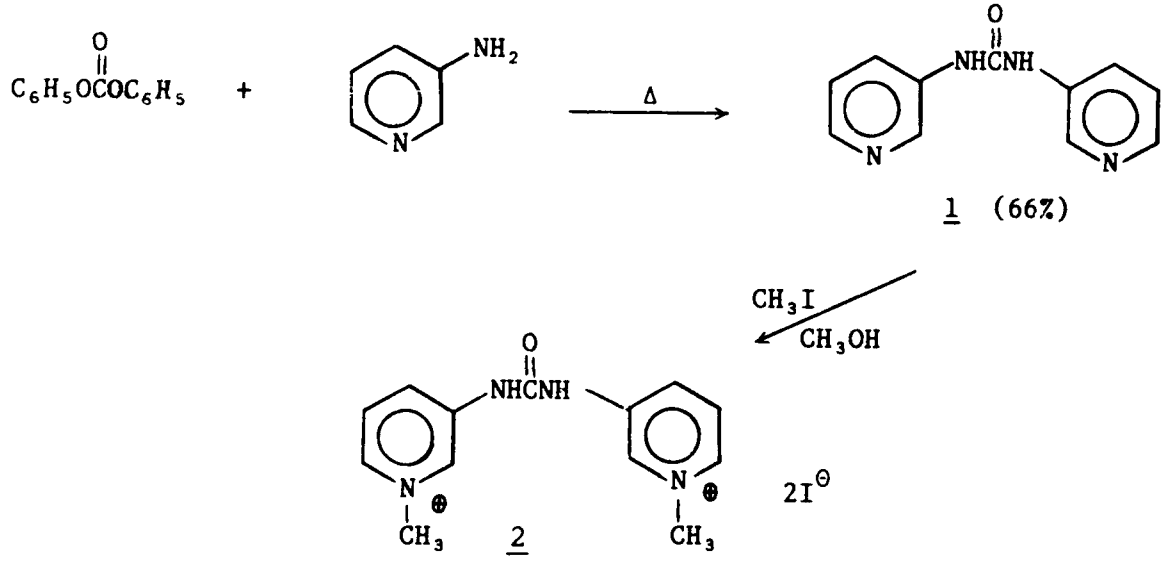
3 (64%)

general literature procedure (35) by the coupling of perfluorobutyllithium, prepared *in situ*, with valeraldehyde. Oxidation of 1 with pyridinium dichromate in methylene chloride gave a satisfactory yield of ketone 2. In the last step, treatment of compound 2 with hydroxylamine gave the desired title oxime 3. NMR spectral evidence indicated that the compound was a mixture of the syn- and anti-oximes (with reference to the perfluorobutyl group) with one of the isomers predominating to the extent of 80-90%. No attempt was made to establish the configuration of the major isomer.

2.57 N,N'-Bis(1-methyl-3-pyridinyl)urea diiodide

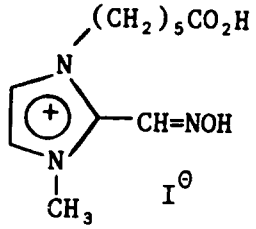


The title compound was prepared by a two-step reaction sequence as shown below.



Thus, diphenyl carbonate was heated with neat 3-aminopyridine to give urea 1. Treatment of compound 1 with excess methyl iodide in methanol solvent gave the title bisquaternary compound 2.

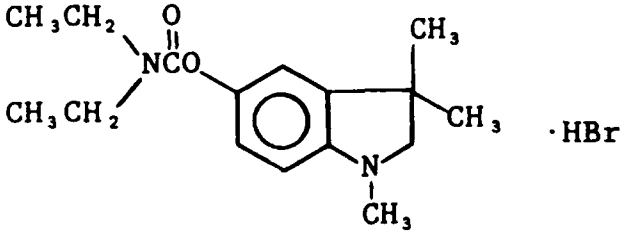
2.58 1-(5-Carboxypentyl)-2-[(hydroxyimino)methyl]-3-methylimidazolium iodide



The title quaternary salt of 2-[(hydroxyimino)methyl]-imidazole was prepared by a three-step synthesis sequence as shown in Chart No. 42. Preparation of carboxaldehyde 1 followed a literature procedure (36) which involved formylation of the lithium salt of N-methylimidazole with dimethylformamide. Aldehyde 1, a low-melting solid, was isolated in 65% yield. Treatment of compound 1 with hydroxylamine hydrochloride in the presence of sodium bicarbonate gave a good yield (73%) of oxime 2.

Quaternarization of compound 2 was attempted initially with 6-bromohexanoic acid. In the presence of a twofold excess of the acid, the reaction proceeded very slowly either in refluxing tetra-hydrofuran, acetone or acetonitrile solvents. Purification of one of the reaction mixtures by cellulose chromatography led to the isolation of a small amount of product identified as the quaternary bromide 3. In view of these poor results, the more reactive 6-iodohexanoic acid was substituted for the bromo acid. This change improved the reaction sufficiently to permit the isolation of crude product 3 in the form of a gummy solid. Purification was accomplished by simple recrystallization; chromatography was not required. Although the product yield was low (22%), it was adequate for the preparation of the requested 10 g of the title target compound.

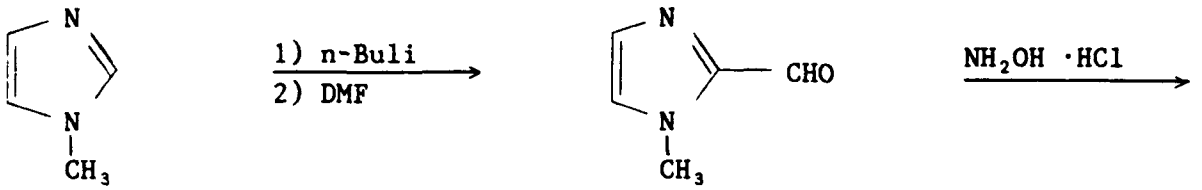
2.59 5-(1,3,3-Trimethylindolinyl)N,N-diethylcarbamate hydrobromide



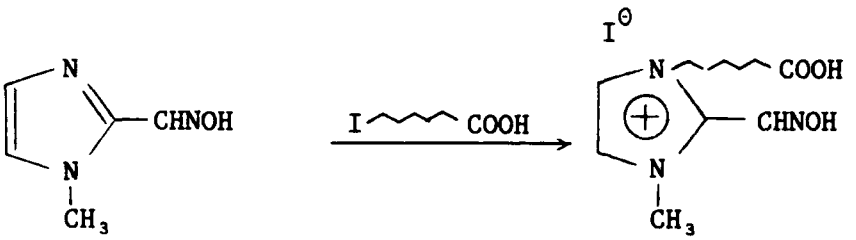
Synthesis of the N,N-dimethylcarbamate analog of the title compound was reported in 1965 by Ahmed and Robinson (37) and more recently by Chinese workers (38,39). The synthesis route used to prepare the desired diethylcarbamate is shown in Chart No. 43 and

CHART NO. 42

1-(5-CARBOXYPENTYL)-2-[(HYDROXYIMINO)METHYL]-3-METHYLIMIDAZOLIUM IODIDE



1 (65%)

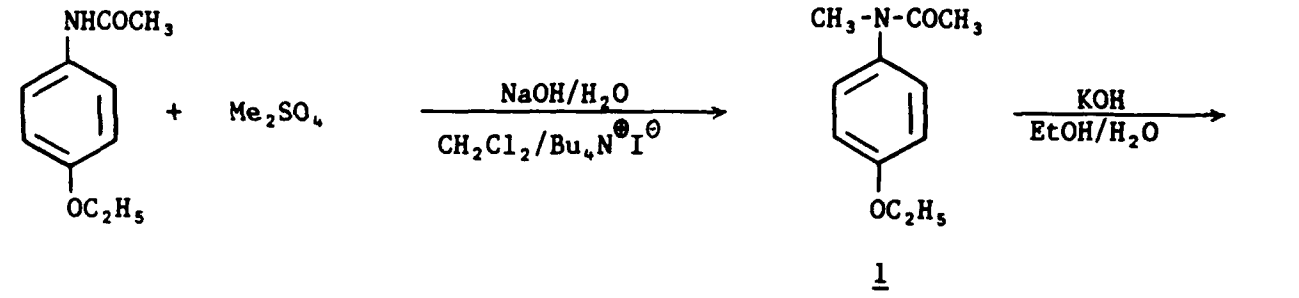


2 (73%)

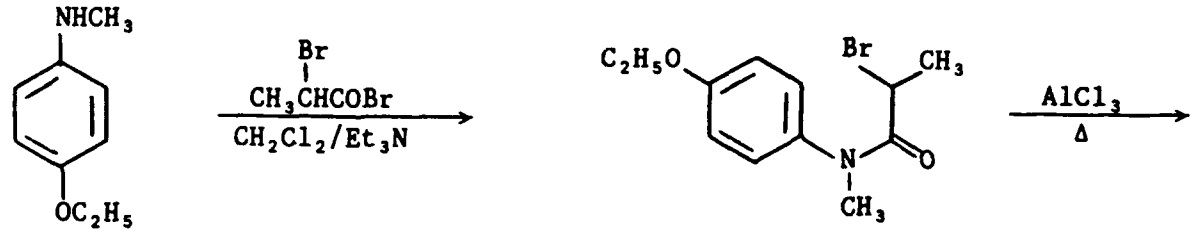
3 (22%)

CHART NO. 43

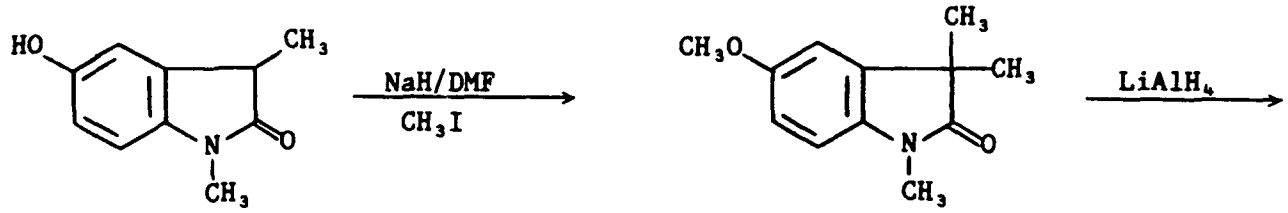
5-(1,3,3-TRIMETHYLINDOLINYL)N,N-DIETHYLCARBAMATE HYDROBROMIDE



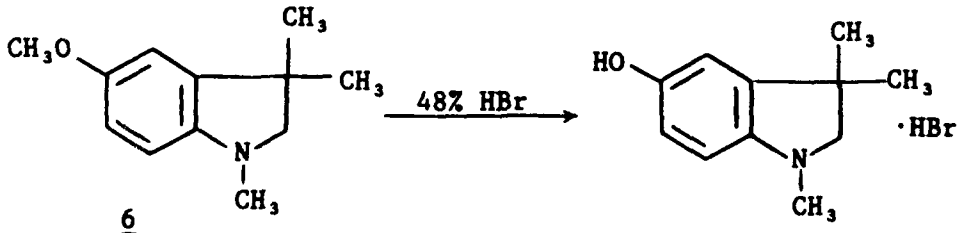
1



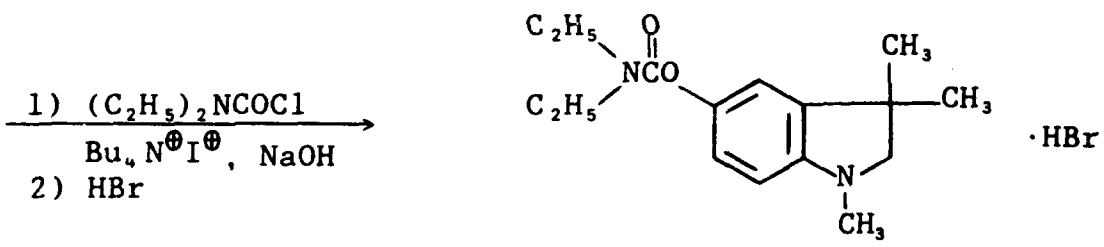
2 3



4 5



6 7



8

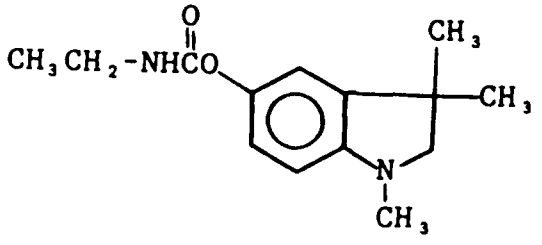
is the same as that described in the literature for closely related indolines (40,41).

N-Acetyl-p-phenetidine was treated with dimethyl sulfate and sodium hydroxide in a water/methylene chloride system using tetrabutylammonium iodide as a phase transfer catalyst to give the N-methylated intermediate 1. Base hydrolysis of the latter in aqueous ethanol gave N-methyl-p-phenetidine (2). Next, compound 2 was treated with α-bromopropionyl bromide to yield the N-acylated intermediate 3. In the literature procedure (40), excess N-methyl-p-phenetidine was used as the acid acceptor, whereas in the current work the readily available and less-expensive triethylamine was the acid acceptor. Crude 3 was isolated in 97% yield and cyclization of compound 3 with aluminum chloride gave 5-hydroxy-2-indolinone 4.

The conversion of 4 to 5 by procedures reported in the literature (40) involved two steps. First, compound 4 was treated with a dialkyl sulfate and aqueous base to give a 5-alkoxy derivative which was treated with methyl iodide and sodium ethoxide to introduce the second methyl group at the 3-position of the indole ring. In the present work, this conversion was accomplished in one step by treating intermediate 4 with sodium hydride and methyl iodide in dimethylformamide as the solvent. Compound 5 was isolated in 67% yield.

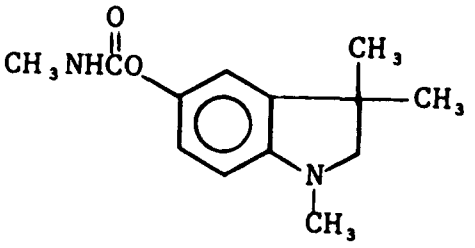
Reduction of the 2-keto group with sodium and n-butanol is reported (41) to give a low yield of the desired product 6. Accordingly, an alternative method (42) using lithium aluminum hydride was employed, and product 6 was isolated in 88% yield. Cleavage of the 5-methoxy group with aqueous hydrobromic acid gave a 95% yield of the crystalline key intermediate 7. Finally, treatment of compound 7 with diethylcarbamoyl chloride and sodium hydroxide in a two-phase system (43) gave the title diethylcarbamate 8, isolated as the hydrobromide salt in 78% yield.

2.60 5-(1,3,3-Trimethylindolinyl)N-ethylcarbamate



The title new carbamate was prepared from intermediate 7 of Chart No. 43, section 2.59. The compound 7, hydrobromide salt, was converted to the free base with sodium carbonate, then treated with ethyl isocyanate and a catalytic amount of sodium metal. The crystalline N-ethylcarbamate was isolated in 74% yield.

2.61 5-(1,3,3-Trimethylindolinyl)N-methylcarbamate



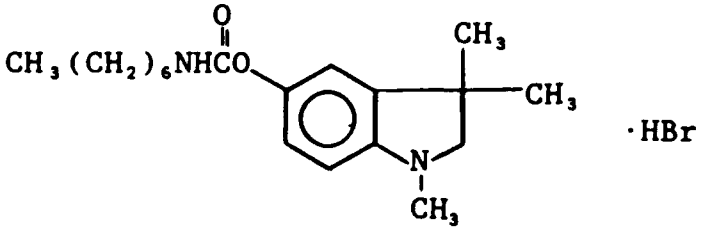
The title N-methylcarbamate was prepared from intermediate 7 of Chart No. 43 in the same manner as the N-ethylcarbamate described above. Thus, treatment of compound 7 free base with methyl isocyanate and catalytic sodium metal gave the crystalline carbamate in 90% yield.

2.62 d_8-Thiodiglycol

$$HOCD_2CD_2SCD_2CD_2OH$$

The title compound was prepared by a general literature procedure (44) used for the synthesis of the radiolabeled product. Hydrogen sulfide was treated with d_4-ethylene oxide at room temperature in the presence of a catalytic amount of sodium methoxide and gave a mixture of d_4-thioglycol and the desired product. The mixture was separated by distillation, and the thioglycol was treated with fresh d_4-ethylene oxide to yield additional product. The overall yield, based on d_4-ethylene oxide, was 65%.

2.63 5-(1,3,3-Trimethylindolinyl)N-heptylcarbamate hydrobromide



The title carbamate was prepared by treating the precursor 5-hydroxyindoline 7 shown in Chart No. 43, section 2.59, with n-heptyl isocyanate. The product was isolated as the crystalline hydrobromide salt in 70% yield.

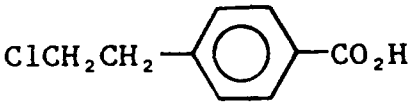
2.64 8-Chlorocaprylic acid

$$ClCH_2(CH_2)_6COOH$$

The synthesis sequence to this compound is shown in Chart No. 44. A shorter route to intermediate 3, i.e., the Baeyer-Villiger oxidation of cyclooctanone with peracetic acid, was considered by us, but it was discarded in view of a 1958 literature article (45) which states that the reaction proceeds in very low yield. A later article describes the successful conversion of cyclooctanone to 8-hydroxyoctanoic acid-lactone using trifluoroperacetic acid (46), but no yields are reported.

Turning to Chart No. 44, monomethyl suberate was treated with thionyl chloride to give acid chloride 1 which was reduced with sodium borohydride to 8-hydroxyoctanoic acid methyl ester (2). The ester was hydrolyzed with alcoholic base and the product, hydroxy acid 3, was treated with thionyl chloride to give 8-chlorocapryloyl chloride (4). Mild base hydrolysis of the acid chloride gave the desired title chloroacid 5.

2.65 4-(2-Chloroethyl)benzoic acid



This assignment entailed a simple purification of commercially available material. Thus, recrystallization of the commercial product from toluene gave analytically pure title acid.

2.66 5-Carboxypentyl trifluoromethyl disulfide

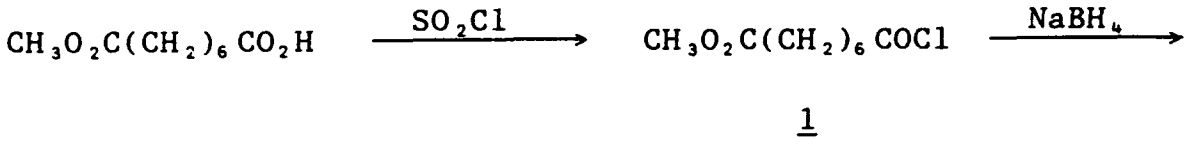
$$F_3CSS(CH_2)_5COOH$$

The title compound represents a new structure not previously reported in the chemical literature.

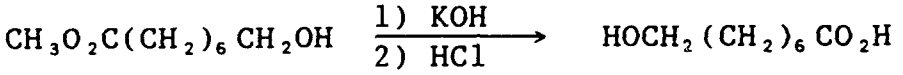
A number of synthesis procedures are available for the preparation of symmetrical disulfides, one of the simplest being the oxidation of thiols with iodine. When applied to the synthesis of unsymmetrical disulfides, these approaches invariably give mixtures of symmetrical and unsymmetrical disulfides. Accordingly, a thorough literature search was carried out in order to find methods useful for the preparation of mixed disulfides. Of the various approaches reported, several appeared applicable to the current problem. The method of

CHART NO. 44

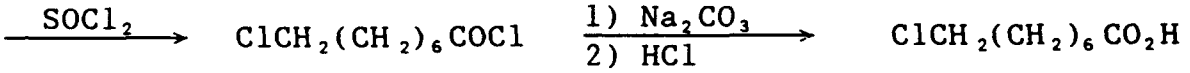
8-CHLOROCAPRYLIC ACID



1



2 3

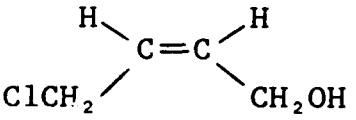


4 5

applicable to the current problem. The method of disulfide bond formation chosen for the current synthesis work is the same as that reported in the literature (47) for the preparation of a similar mixed disulfide.

The overall synthesis route is shown in Chart No. 45. The required precursor, compound 1, was prepared by the treatment of 6-bromohexanoic acid with thiourea to give a thiouronium salt which was hydrolyzed directly with sodium hydroxide to 6-mercaptohexanoic acid. Next, the thioacid 1 was coupled with trifluoromethylsulfenyl chloride in methylene chloride as solvent. Thin-layer chromatography showed the formation of one major product contaminated with two impurities (the symmetrical disulfides). Purification was accomplished readily by distillation, and pure product 2 was obtained in 57% yield.

2.67 cis-4-Chloro-2-buten-1-ol



The title compound was prepared by a literature procedure (48) whereby cis-2-butene-1,4-diol was treated with one equivalent of thionyl chloride in the presence of pyridine. The product was purified by column chromatography and distillation. Although the product yield was low, sufficient material was obtained to fill the order; no effort was made to improve the yield.

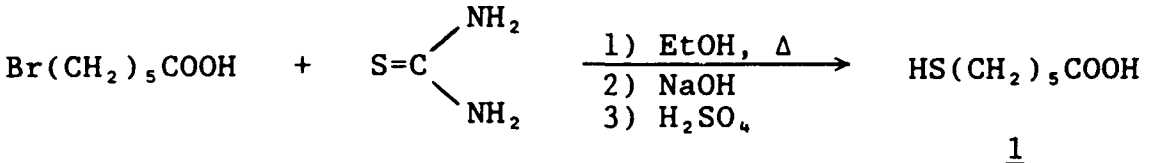
2.68 Sodium ethanethiosulfonate

$$CH_3CH_2SO_2SNa$$

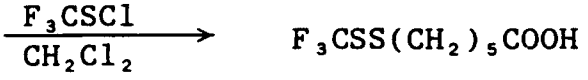
Preparation of the crystalline anhydrous potassium salt as well as the monohydrated sodium salt has been reported in the literature (49,50). For the current work, the same synthesis approach was used which involved the reaction of ethanesulfonyl chloride with aqueous sodium sulfide. Recrystallization of the crude product from ethanol gave pure anhydrous title compound. Recrystallization from water is reported to give monohydrated product (50).

CHART NO. 45

5-CARBOXYPENTYL TRIFLUOROMETHYL DISULFIDE



1



2

2.69 Thiotaurine

$$H_2NCH_2CH_2SO_2SH$$

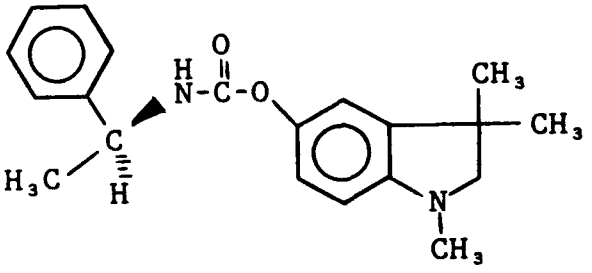
The title compound was prepared by a standard literature procedure (51) as outlined in Chart No. 46. Thus, treatment of 2-aminoethanethiol hydrochloride with hydrogen peroxide in the presence of potassium iodide catalyst gave 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (1). Compound 1 was dissolved in sodium hydroxide and applied to a column of Dowex 1-X2 ion-exchange resin. After washing with water, the column was eluted carefully with hydrochloric acid to give hypotaurine (2). Finally, treatment of intermediate 2 with elemental sulfur in ethanol solvent containing some sodium hydroxide gave the desired title target structure 3.

2.70 Sodium 1-propanethiosulfonate

$$CH_3CH_2CH_2SO_2SNa$$

Synthesis of the potassium salt of 1-propanethiosulfonic acid has been reported in the literature (52). The title sodium salt was prepared by the same general procedure. Thus, treatment of 1-propanesulfonyl chloride with sodium sulfide in aqueous dimethoxyethane gave crude title product which was purified by recrystallization. No attempt was made to optimize product yield.

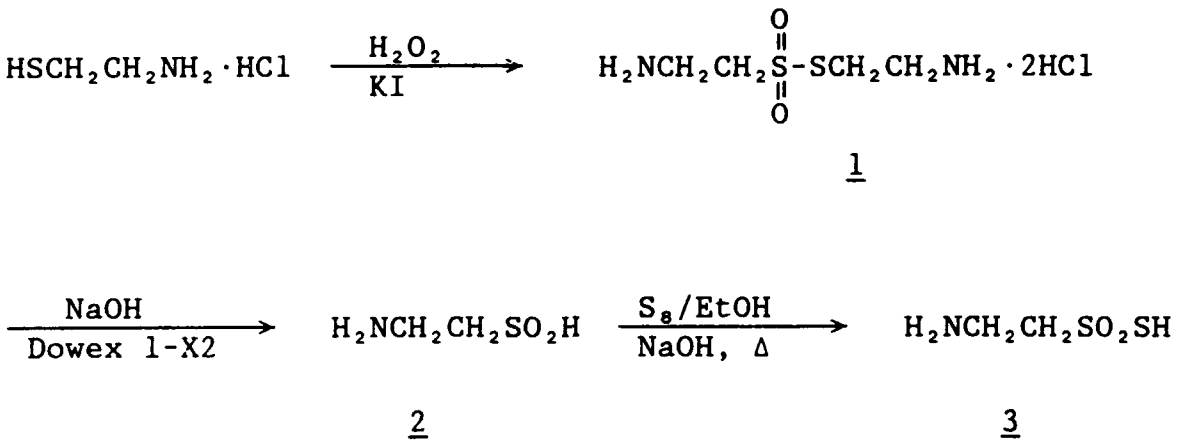
2.71 (S)(-)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)-carbamate



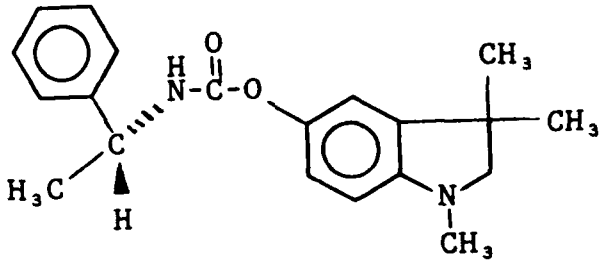
The title carbamate was prepared from intermediate 7 of Chart No. 43, section 2.59. A sample of this intermediate was converted with sodium carbonate to the free base, then treated with (S)(-)-1-phenylethyl isocyanate to yield the title carbamate. The yield of pure product was only fair (45%), but more emphasis was placed on product purity than yield.

CHART NO. 46

THIOTAURINE

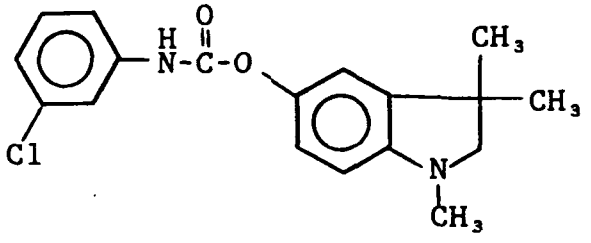


2.72 (R)(+)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)-carbamate



The title carbamate was prepared in the same manner as the enantiomer described in section 2.71 by treating intermediate 7, free base, of Chart No. 43, section 2.59, with (R)(+)-1-phenylethyl isocyanate. Pure product was isolated in 54% yield.

2.73 5-(1,3,3-Trimethylindolinyl)-N-(3-chlorophenyl)carbamate



The title carbamate was prepared by treating intermediate 7, free base of Chart No. 43, section 2.59, with 3-chlorophenyl isocyanate. The yield of pure product was 73%.

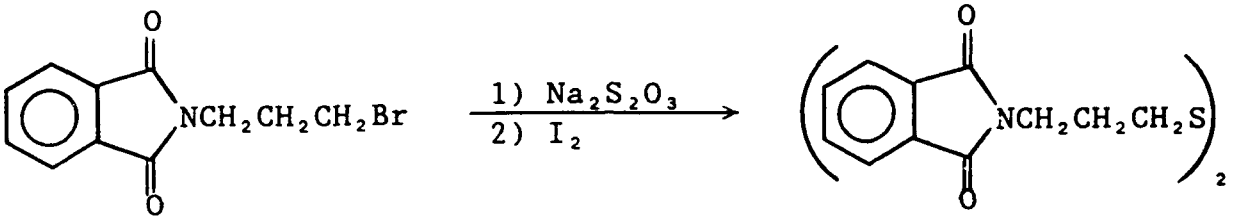
2.74 Homothiotaurine

$$H_2NCH_2CH_2CH_2SO_2SH$$

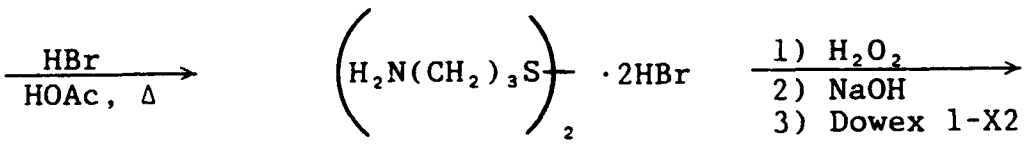
Synthesis of homothiotaurine has been reported in the literature (53). The same general route, outlined in Chart No. 47, was used in the current work. Compound 1 was prepared by the successive treatment of N-(3-bromopropyl)phthalimide with sodium thiosulfate and iodine (54). Acid hydrolysis of this intermediate gave homocystamine dihydrobromide (2). Next, compound 2 was oxidized with hydrogen peroxide to a thiol-sulfonate which was then cleaved with sodium hydroxide to homohypotaurine (3). By the literature procedure (53), the thiolsulfonate intermediate is not isolated but is treated directly with base to give compound 3 which is purified by chromatography over Dowex 50 ion-exchange resin. In the current work, crude thiolsulfonate dihydrobromide was isolated in the form of a crystalline solid, then treated with base and passed

CHART NO. 47

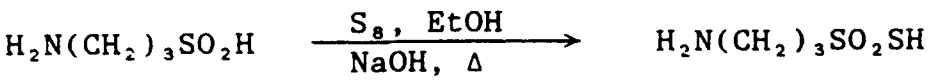
HOMOTHIOTAURINE



1



2



3 4

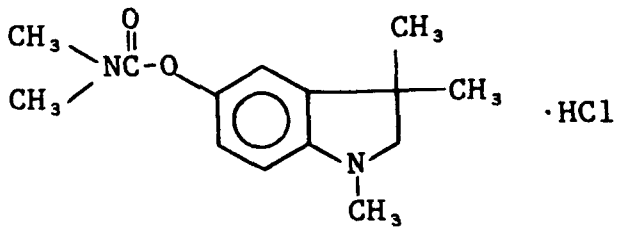
over a Dowex 1-X2 ion exchange resin to give compound 3. In the last step, sulfinic acid 3 was treated with elemental sulfur in ethanol solvent containing some aqueous sodium hydroxide to yield the title target compound 4.

2.75 4-Chlorobutanol

$$ClCH_2CH_2CH_2CH_2OH$$

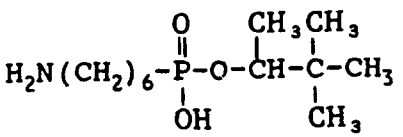
This assignment entailed the purification of commercially available material. Thus, technical 4-chlorobutanol (85%) was dried over potassium carbonate, then it was distilled through a five-plate bubble plate column. The product analyzed for 99% 4-chloro-butanol containing 1% water.

2.76 5-(1,3,3-Trimethylindolinyl)-N,N-dimethylcarbamate hydrochloride



Preparation of the title compound has been reported in the literature (37,38). For the current synthesis, compound 7 of Chart No. 43, section 2.59 was treated with dimethylcarbamoyl chloride in a two-phase system to give the title target structure, which was purified and characterized as a hydrochloride salt. The melting point of our product differs from that reported originally (37), but it is in agreement with the melting point reported in a later article (38). The elemental analysis and spectral data are in good agreement with the dimethylcarbamate structure.

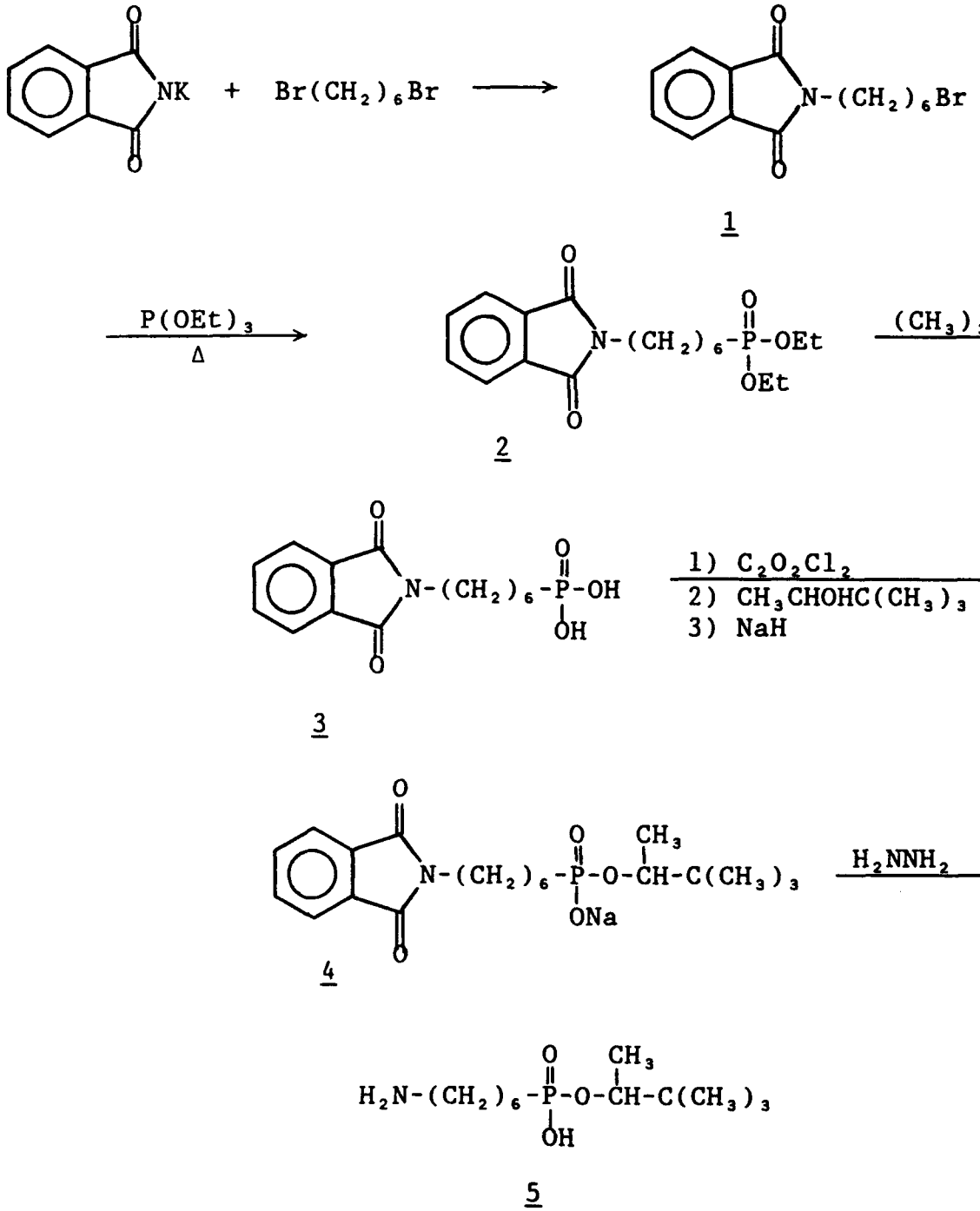
2.77 6-Aminohexylphosphonic acid monopinacolyl ester



The title compound represents a new structure not reported in the chemical literature. The synthesis was accomplished via a five-step sequence as outlined in Chart No. 48.

CHART NO. 48

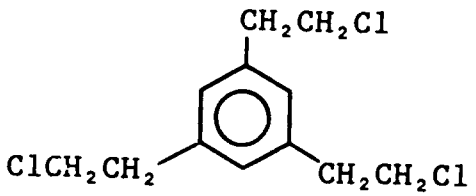
6-AMINOHEXYLPHOSPHONIC ACID, MONOPINACOLYL ESTER



6-Bromohexylphthalimide (1) was prepared by the reaction of 1,6-dibromohexane with potassium phthalimide (55). Treatment of compound 1 with excess triethyl phosphite at near reflux temperature gave the phosphonate ester 2.

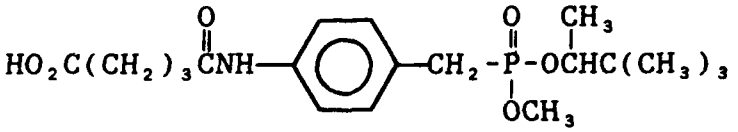
In the next step, hydrolysis of ester 2 with acid or base was avoided in order to prevent the loss of the phthalimide. Instead, the ethyl groups were cleaved selectively with trimethylsilyl bromide to give phosphonic acid 3. Compound 3 was converted to a monochloridate with oxaloyl chloride, then esterified with pinacolyl alcohol to give a monopinacolyl ester, isolated as the sodium salt 4. In the last step, the phthalimide was cleaved with hydrazine to give the title target phosphinic acid 5. Thin-layer chromatography indicated that compound 5 was the major reaction product. However, purification of the crude material proved to be quite tedious and pure 5 was isolated in 14% yield. A sufficient quantity of pure product was obtained to fill the request; accordingly, no attempt was made to optimize the yield.

2.78 1,3,5-Tris-2'-chloroethylbenzene



Synthesis of the title compound has been reported in the literature (56). The same approach, outlined in Chart No. 49, was used in the current work. By this route, 1,3,5-triacetylbenzene was treated with morpholine and sulfur to give the triacetic acid 1. Compound 1 was esterified with ethanol and the resulting triester 2 was reduced with lithium aluminum hydride to triol 3. Treatment of compound 3 with thionyl chloride and pyridine gave the desired title target compound 4.

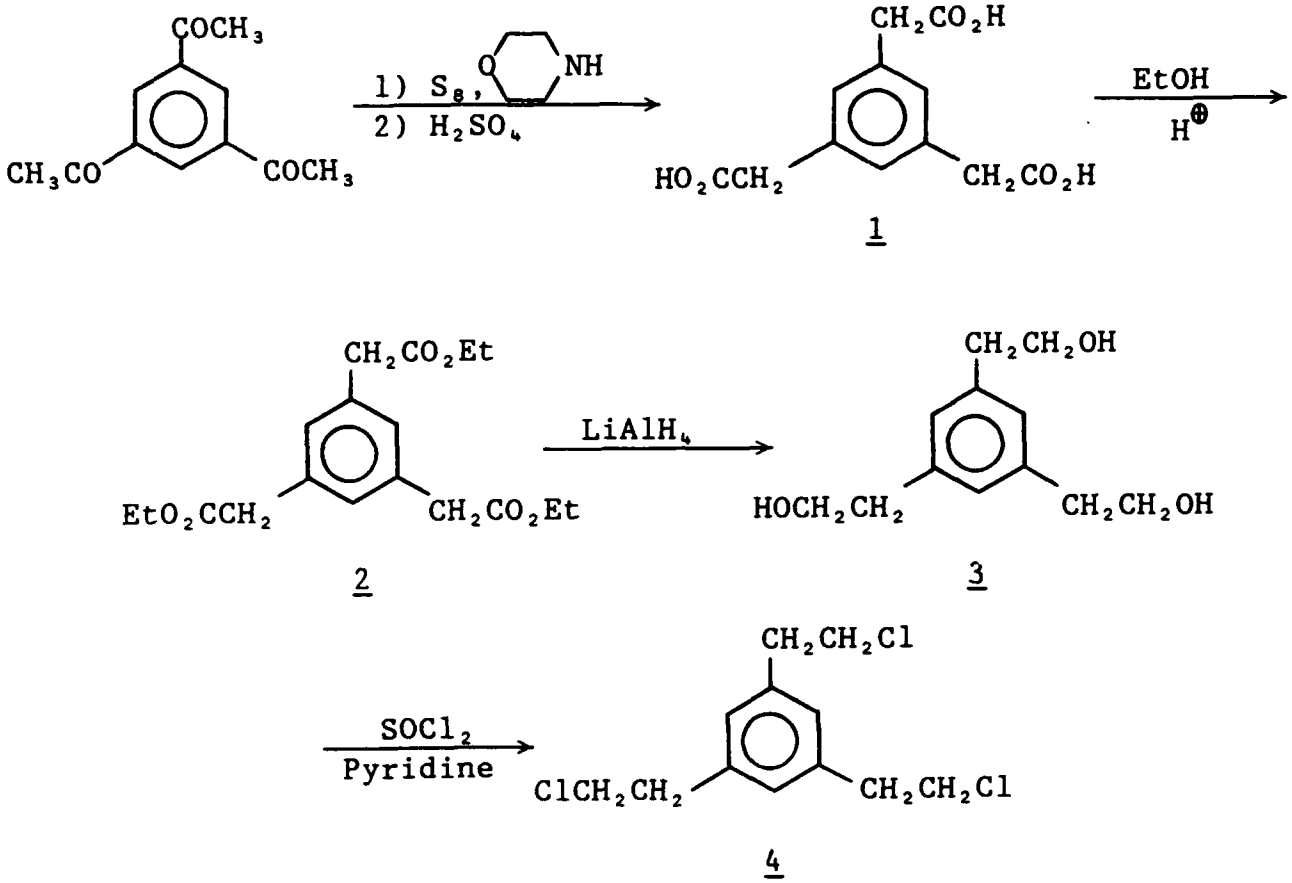
2.79 Methyl pinacolyl 4-(4-carboxybutanoylamino)benzylphosphonate



Synthesis of the title benzylphosphonic acid mono-α-phenethyl ester by a seven-step reaction sequence has been reported in the literature (57). Although the reaction

CHART NO. 49

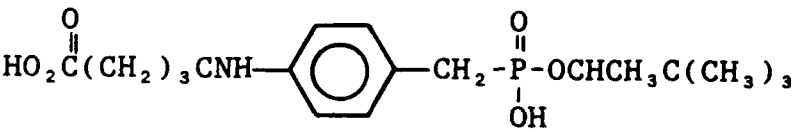
1,3,5-TRIS-2'-CHLOROETHYLBENZENE



conditions were given for each step, a detailed experimental procedure was not presented. The above methyl pinacolyl ester was synthesized via the same general sequence as shown in Chart No. 50.

Referring to Chart No. 50, diethyl 4-aminobenzylphosphonate was treated with trifluoroacetic anhydride to give the trifluoroacetamide 1. Next, the ethyl ester was cleaved by successive treatment with trimethylsilyl bromide and water to give phosphonic acid 2. Conversion of acid 2 to the dimethyl ester 3 was effected in the initial small-scale runs with diazomethane. In a subsequent larger-scale preparation, the procedure was changed in that the acid was treated first with phosphorus pentachloride to give a phosphonodichloridate which was then converted to ester 3 by the action of lithium methoxide in methanol. Treatment of phosphono diester 3 with one equivalent of phosphorus pentachloride converted it to a phosphonomonochloridate. The reaction of this acid chloride with the lithium salt of pinacolyl alcohol gave the mixed ester 4. The protecting trifluoroacetyl group was selectively removed with sodium borohydride and the resulting amine was treated with glutaric anhydride to give the title target compound 5.

2.80 Monopinacolyl 4-(4-carboxybutanoylamino)benzylphosphonate

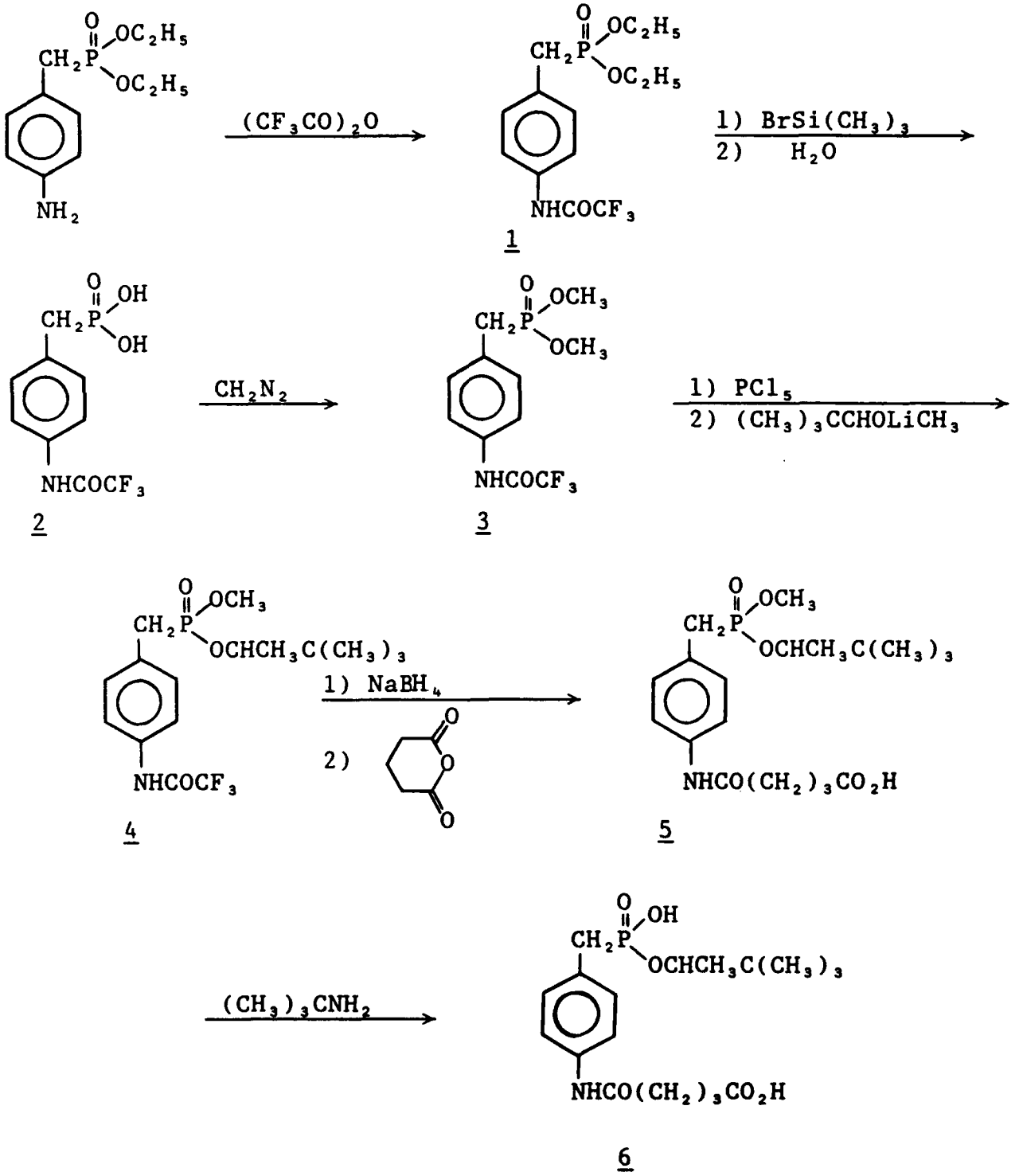


The title phosphonic acid monoester was prepared as shown in Chart No. 50 by the selective hydrolysis of the mixed diester described in section 2.79 above. Thus, diester 5 was treated with tert-butylamine in acetonitrile at 55-60°C for 11 days to give monoester 6 as a tert-butylamine salt. Thin-layer chromatography (TLC) showed that this material was contaminated with a minor impurity which could not be removed by recrystallization. Passage of a small sample of this salt over ion exchange resin gave pure free acid 6 as a crystalline solid. However, treatment of the remaining salt, in methanol, with the ion exchange resin converted the carboxy group to a methyl ester. Accordingly, this material was treated with sodium carbonate to hydrolyze the carboxylic ester, then acidified with hydrochloric acid to give crude product 6. One recrystallization gave pure title phosphonic acid, monopinacolyl ester.

CHART NO. 50

METHYL PINACOLYL AND MONOPINACOLYL

4-(4-CARBOXYBUTANOYLAMINO)BENZYLPHOSPHONATE



1

2

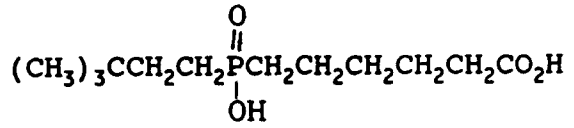
3

4

5

6

2.81 (5-Carboxypentyl)(3,3-dimethylbutyl)phosphinic acid



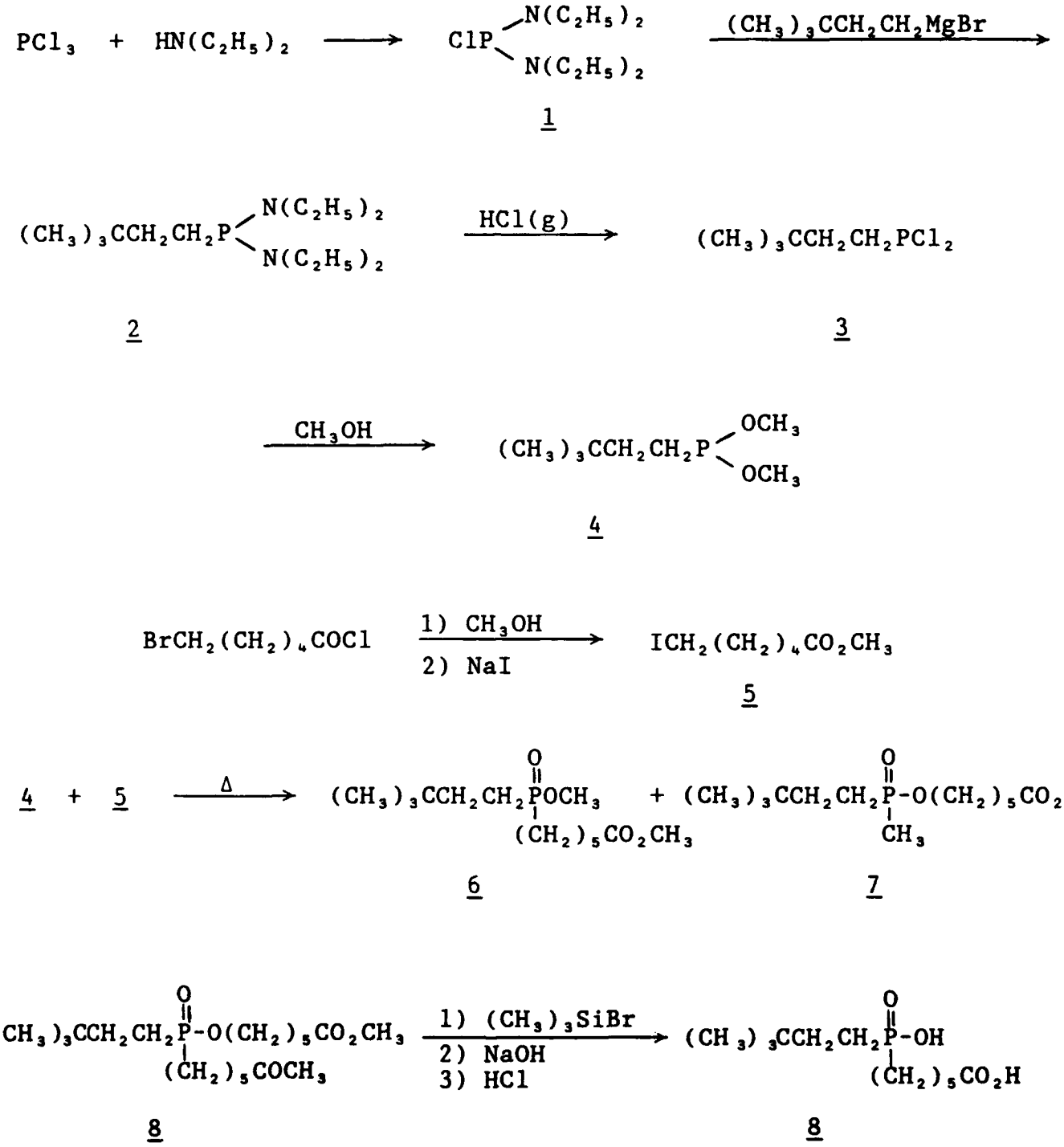
The title compound is a new structure not reported in the chemical literature. Synthesis of this target was accomplished as shown in Chart No. 51.

The phosphorodiamidous chloride 1 was prepared by a literature procedure (58). Treatment of compound 1 with 3,3-dimethylbutylmagnesium bromide gave the phosphonous diamide 2. Cleavage of the diethylamide groups was accomplished readily with anhydrous hydrogen chloride, and the product, phosphonous dichloride 3, was converted to dimethyl phosphonite 4 by treatment with methanol and triethylamine. It was essential to handle compound 4 in an inert atmosphere, since it is readily oxidized in air to dimethyl 3,3-dimethylbutylphosphonate. Methyl 6-iodo-hexanoate was prepared from 6-bromohexanoyl chloride by treatment with methanol followed by sodium iodide in acetone. Next, phosphonite 4 was subjected to the Arbuzov reaction with iodohexanoate 5 to give a mixture of phosphinates 6 and 7. Attempts to improve product yield and purity were not successful. Variables studied included reaction time and temperature and the method of addition of the iodoester. Formation of phosphinate ester 7 was observed early in the reaction. Increasing the temperature or reaction time to drive the reaction to completion aided the formation of the undesired ester 7 and other impurities, including compound 8. Accordingly, the mixture of 6 and 7 was carried on to product 9. Successive treatment of the mixture with trimethylsilyl bromide and sodium hydroxide cleaved the ester groups to give product 9, isolated as the free acid and purified by recrystallization.

The synthesis sequence was satisfactory for the preparation of a 5 g sample of compound 9. For larger scale syntheses, improvements in the sequence would have to be made.

CHART NO. 51

(5-CARBOXYPENTYL)(3,3-DIMETHYLBUTYL)PHOSPHINIC ACID



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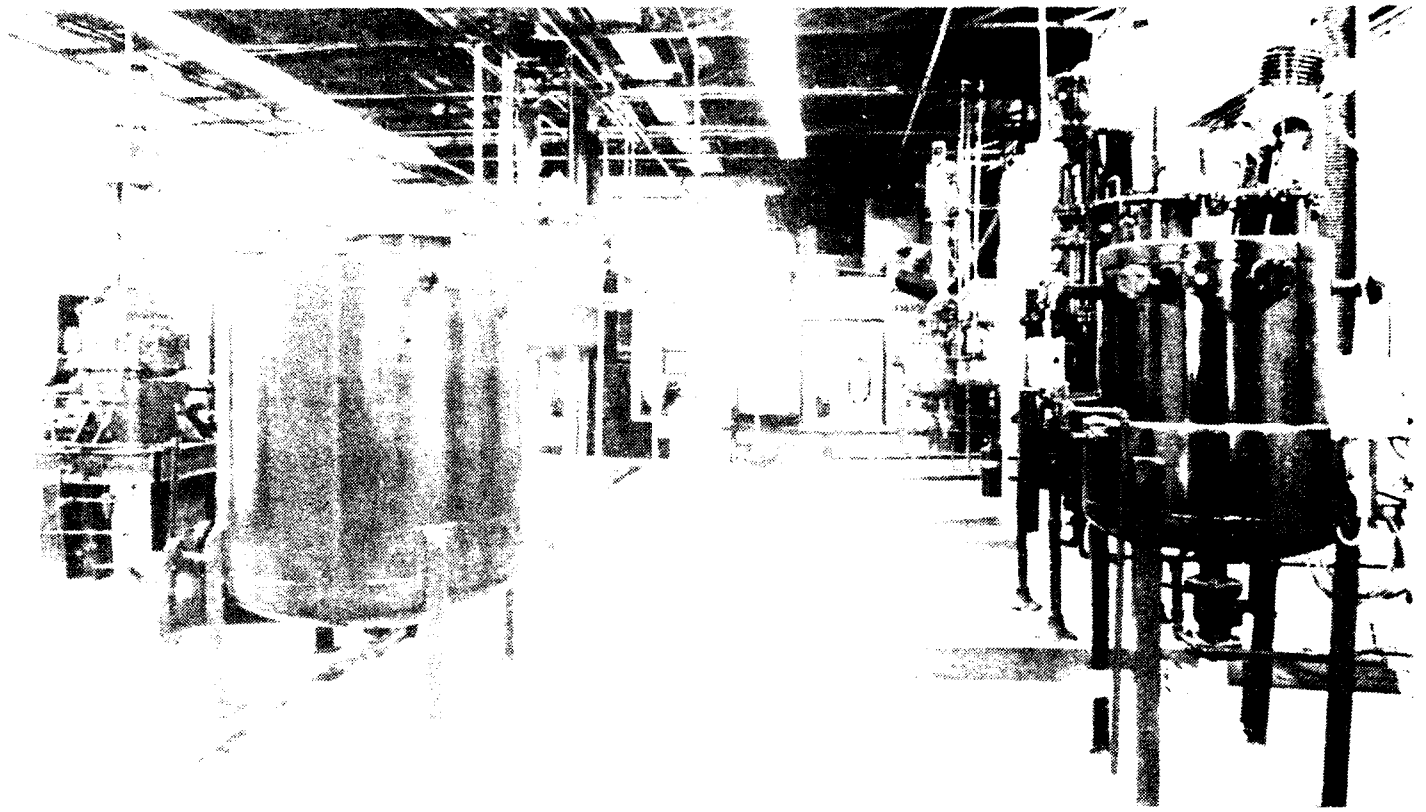

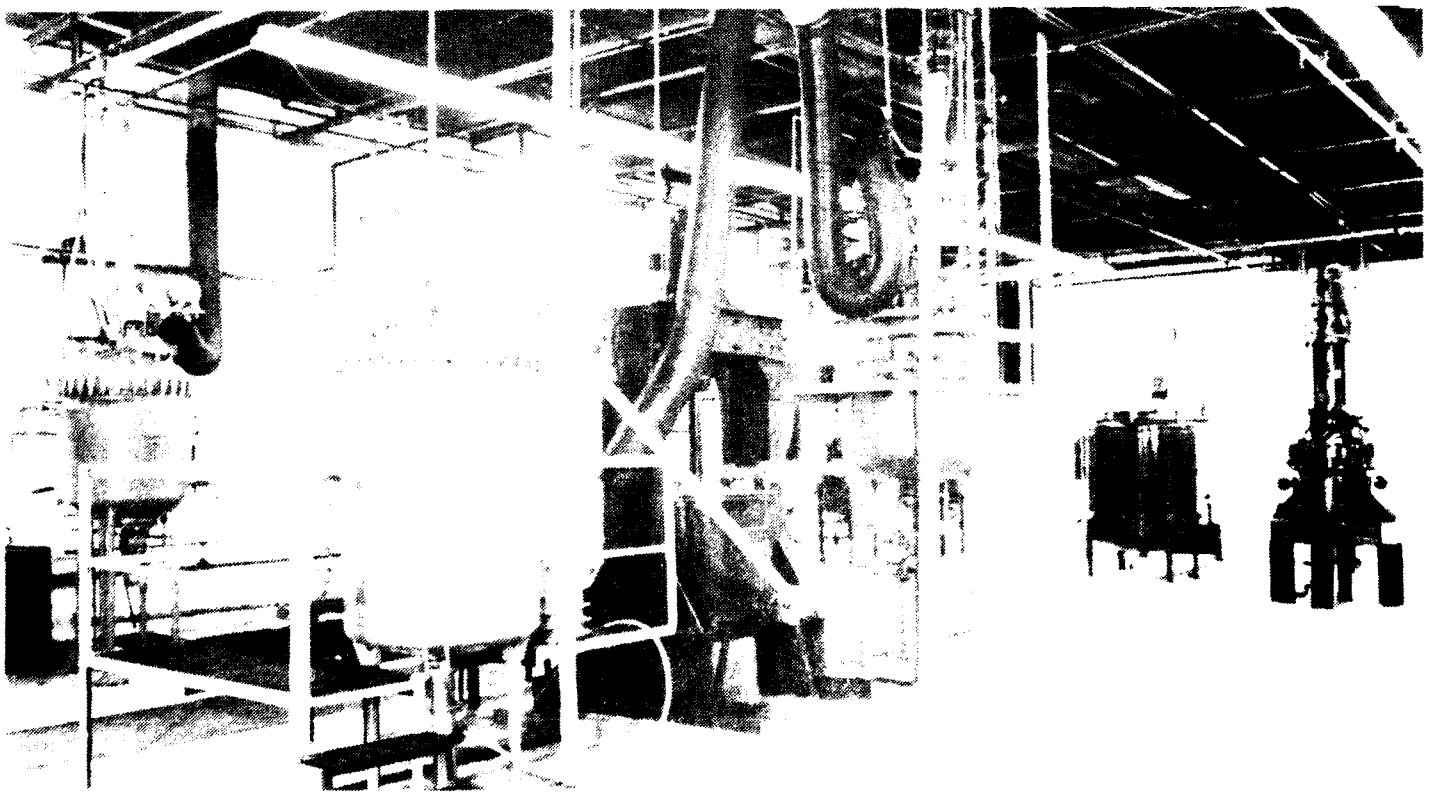

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